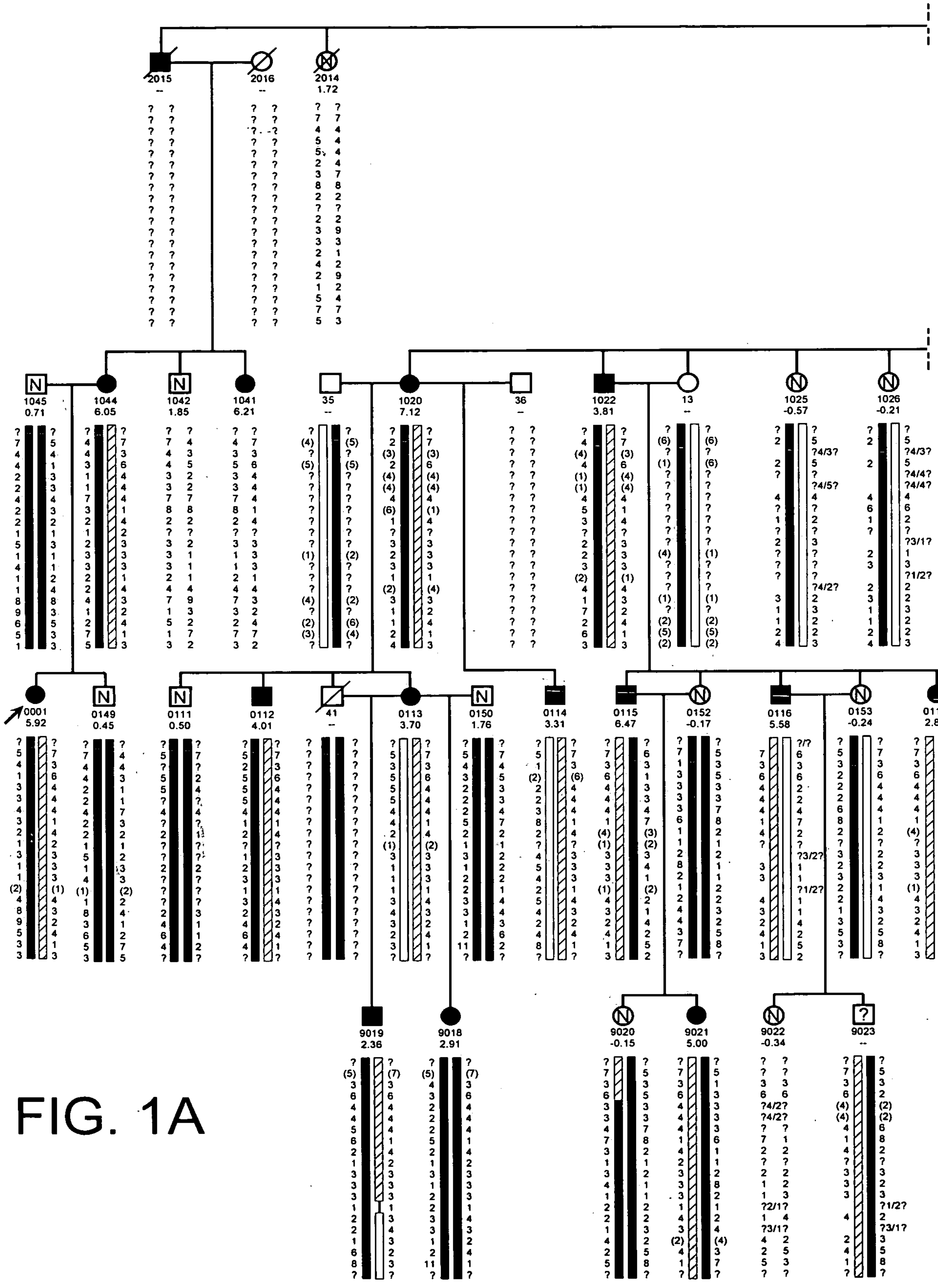

2015
--
2016
--
2014
1.72
N
1045
0.71
1044
6.05
N
1042
1.85
1041
6.21
35
--
1020
7.12
36
--
1022
3.81
13
--
N
1025
-0.57
N
1026
-0.21
0001
5.92
N
0149
0.45
N
0111
0.50
0112
4.01
41
--
0113
3.70
N
0150
1.76
0114
3.31
0115
6.47
N
0152
-0.17
0116
5.58
N
0153
-0.24
0117
2.85
9019
2.36
9018
2.91
N
9020
-0.15
9021
5.00
N
9022
-0.34
?
9023
--

FIG. 1A

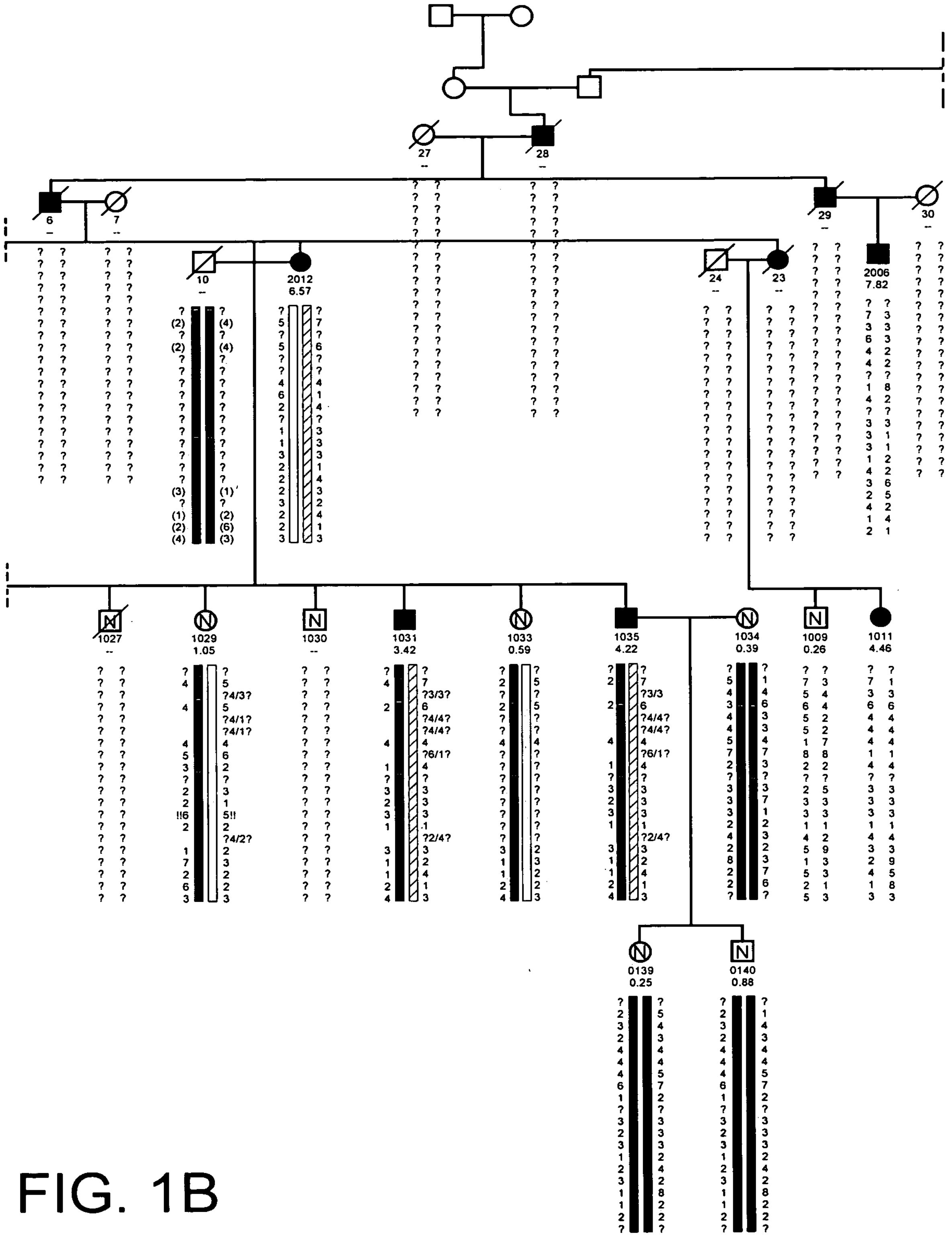

27
28
6
7
29
30
10
2012
6.57
24
23
2006
7.82
1027
1029
1.05
1030
1031
3.42
1033
0.59
1035
4.22
1034
0.39
1009
0.26
1011
4.46
0139
0.25
0140
0.88
N

FIG. 1B

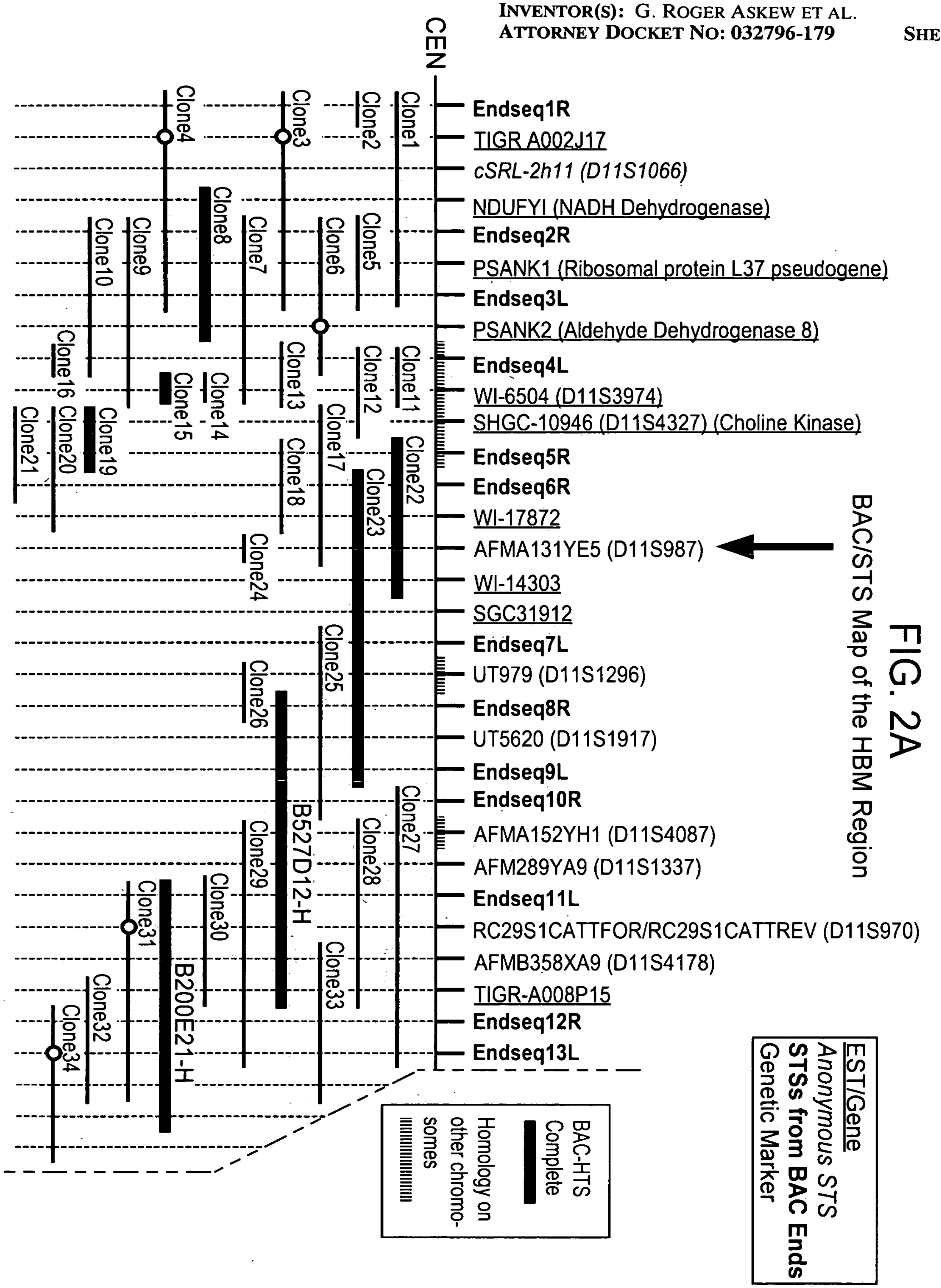


FIG. 2A

BAC/STS Map of the HBM Region

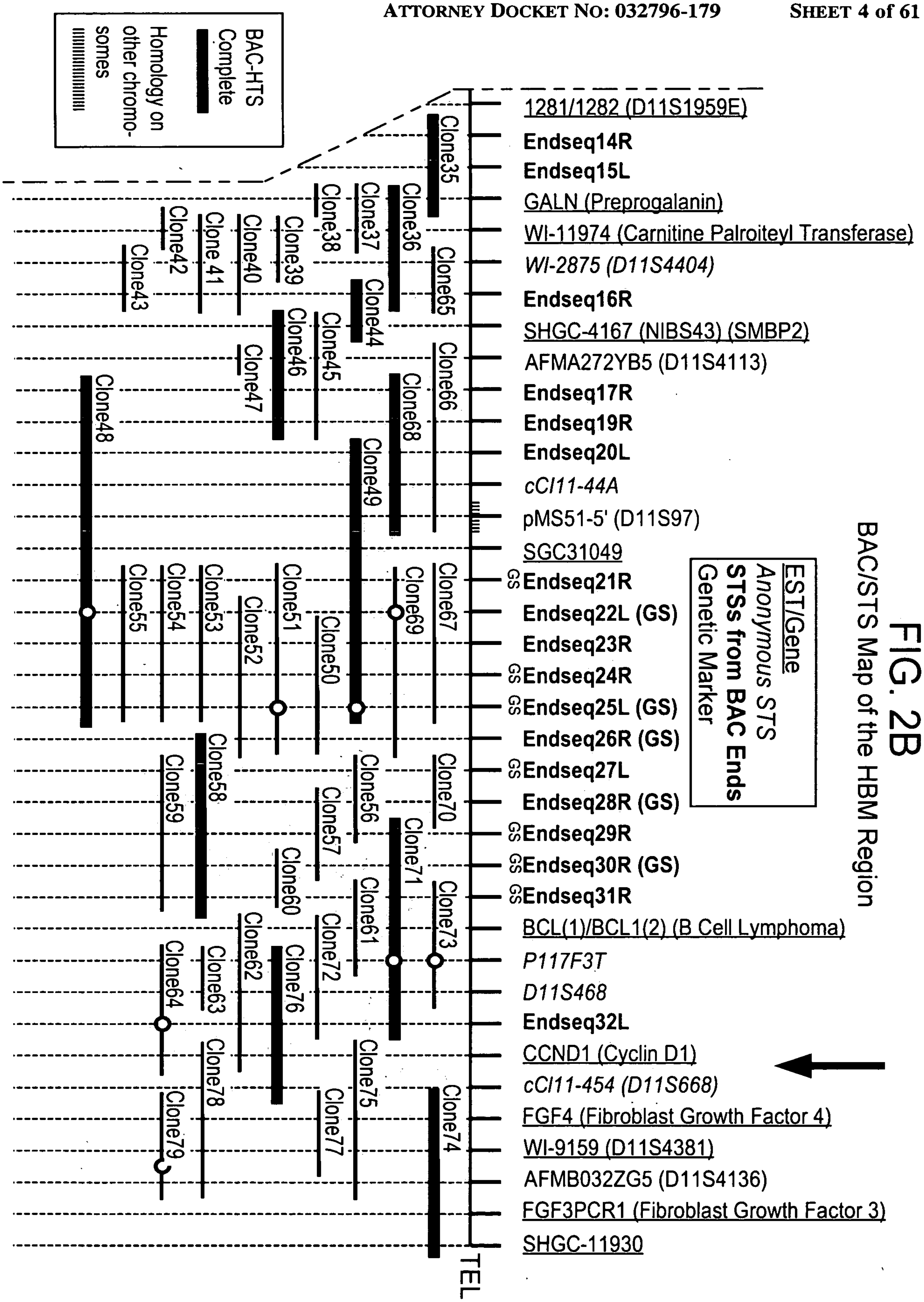


FIG. 2B
BAC/STS Map of the HBM Region

Exon 1
ACTAAAGCGCCGCCGCCGCGCCATGGAGCCCGAGTGAGCGCGGCGCGG
GCCCGTCCGGCCGCCGGACAACATGGAGGCAGCGCCGCCCGGGCCGCC
GTGGCCGCTGCTGCTGCTGCTGCTGCTGCTGCTGGCGCTGTGCGGCTGC
CCGGCCCCCGCCGCGGCC

Exon 2 Coordinates: 527d12_Contig308G 30944-30549
gccccacag**CCTCGCCGCTCCTGCTATTTGCCAACCGCCGGGACGTACGGCT**
GGTGGACGCCGGCGGAGTCAAGCTGGAGTCCACCATCGTGGTCAGCGG
CCTGGAGGATGCGGCCGCAGTGGACTTCCAGTTTTCCAAGGGAGCCGTG
TACTGGACAGACGTGAGCGAGGAGGCCATCAAGCAGACCTACCTGAACC
AGACGGGGGCCGCCGTGCAGAACGTGGTCATCTCCGGCCTGGTCTCTCC
CGACGGCCTCGCCTGCGACTGGGTGGGCAAGAAGCTGTACTGGACGGA
CTCAGAGACCAACCGCATCGAGGTGGCCAACCTCAATGGCACATCCCGG
AAGGTGCTCTTCTGGCAGGACCTTGACCAGCCGAGGGCCATCGCCTTGG
ACCCCGCTCACGGgtaaaccctgctg

... 9408 nt ...

Exon 3 Coordinates: 527d12_Contig308G 21141-20945
ccccgtcacag**GTACATGTACTGGACAGACTGGGGTGAGACGCCCCGGATTGA**
GCGGGCAGGGATGGATGGCAGCACCCGGAAGATCATTGTGGACTCGGA
CATTTACTGGCCCAATGGACTGACCATCGACCTGGAGGAGCAGAAGCTC
TACTGGGCTGACGCCAAGCTCAGCTTCATCCACCGTGCCAACCTGGACG
GCTCGTTCCGgtaggtacccac

... 6094 nt ...

Exon 4 Coordinates: 527d12_Contig308G 15047-14850
tccctgactgcag**GCAGAAGGTGGTGGAGGGCAGCCTGACGCACCCCTTCGCCC**
TGACGCTCTCCGGGGACACTCTGTACTGGACAGACTGGCAGACCCGCTC
CATCCATGCCTGCAACAAGCGCACTGGGGGGAAGAGGAAGGAGATCCTG
AGTGCCCTATACTCACCCATGGACATCCAGGTGCTGAGCCAGGAGCGGC
AGCCTTTCTgtgagtgccgg

... 1827 nt ...

Exon 5 Coordinates: 527d12_Contig308G 13220-13088
tttctcag**TCCACACTCGCTGTGAGGAGGACAATGGCGGCTGCTCCCACCTGT**
GCCTGCTGTCCCCAAGCGAGCCTTTCTACACATGCGCCTGCCCCACGGG
TGTGCAGCTGCAGGACAACGGCAGGACGTGTAAGGCAGgtgaggcggtgggacg

FIG. 3A

... 20923 nt ...

Exon 6 Coordinates: 527d12_Contig309G 7705-8100
ctccacag**GAGCCGAGGAGGTGCTGCTGCTGGCCCGGCGGACGGACCTACG**
GAGGATCTCGCTGGACACGCCGGACTTCACCGACATCGTGCTGCAGGTG
GACGACATCCGGCACGCCATTGCCATCGACTACGACCCGCTAGAGGGCT
ATGTCTACTGGACAGATGACGAGGTGCGGGCCATCCGCAGGGCGTACCT
GGACGGGTCTGGGGCGCAGACGCTGGTCAACACCGAGATCAACGACCC
CGATGGCATCGCGGTCGACTGGGTGGCCCGAAACCTCTACTGGACCGAC
ACGGGCACGGACCGCATCGAGGTGACGCGCCTCAACGGCACCTCCCGCA
AGATCCTGGTGTCGGAGGACCTGGACGAGCCCCGAGCCATCGCACTGCA
CCCCGTGATGGGgtaagacgggc

….. 3211 nt …..

Exon 7 Coordinates: 527d12_Contig309G 11311-11482
ttcttctccag**CCTCATGTACTGGACAGACTGGGGAGAGAACCCTAAAATCGAG**
TGTGCCAACTTGGATGGGCAGGAGCGGCGTGTGCTGGTCAATGCCTCCC
TCGGGTGGCCCAACGGCCTGGCCCTGGACCTGCAGGAGGGGAAGCTCT
ACTGGGGAGACGCCAAGACAGACAAGATCGAGgtgaggctcctgtgg

…… 13445 nt …..

Exon 8 Coordinates: 527d12_Contig309G 24927-25143
ccgtcctgcag**GTGATCAATGTTGATGGGACGAAGAGGCGGACCCTCCTGGAG**
GACAAGCTCCCGCACATTTTCGGGTTCACGCTGCTGGGGGACTTCATCT
ACTGGACTGACTGGCAGCGCCGCAGCATCGAGCGGGTGCACAAGGTCAA
GGCCAGCCGGGACGTCATCATTGACCAGCTGCCCGACCTGATGGGGCTC
AAAGCTGTGAATGTGGCCAAGGTCGTCGgtgagtccgggggtc

….2826 nt ……

Exon 9 Coordinates: 527d12_Contig309G 27969-28256
gttcgcttccag**GAACCAACCCGTGTGCGGACAGGAACGGGGGGTGCAGCCACC**
TGTGCTTCTTCACACCCCACGCAACCCGGTGTGGCTGCCCCATCGGCCT
GGAGCTGCTGAGTGACATGAAGACCTGCATCGTGCCTGAGGCCTTCTTG
GTCTTCACCAGCAGAGCCGCCATCCACAGGATCTCCCTCGAGACCAATA
ACAACGACGTGGCCATCCCGCTCACGGGCGTCAAGGAGGCCTCAGCCCT
GGACTTTGATGTGTCCAACAACCACATCTACTGGACAGACGTCAGCCTG
AAGgtagcgtgggc

……3102…..

FIG. 3B

Exon 10 Coordinates: 527d12_Contig309G 31358-31582
cctgctgccag**ACCATCAGCCGCGCCTTCATGAACGGGAGCTCGGTGGAGCAC**
GTGGTGGAGTTTGGCCTTGACTACCCCGAGGGCATGGCCGTTGACTGGA
TGGGCAAGAACCTCTACTGGGCCGACACTGGGACCAACAGAATCGAAGT
GGCGCGGCTGGACGGGCAGTTCCGGCAAGTCCTCGTGTGGAGGGACTT
GGACAACCCGAGGTCGCTGGCCCTGGATCCCACCAAGGGgtaagtgtttgcctgtc

......1297 nt......

Exon 11 Coordinates: 527d12_Contig309G 32879-33064
gtgccttccag**CTACATCTACTGGACCGAGTGGGGCGGCAAGCCGAGGATCGT**
GCGGGCCTTCATGGACGGGACCAACTGCATGACGCTGGTGGACAAGGTG
GGCCGGGCCAACGACCTCACCATTGACTACGCTGACCAGCGCCTCTACT
GGACCGACCTGGACACCAACATGATCGAGTCGTCCAACATGCTGGgtgaggg
ccgggct

.......2069 nt.....

Exon 12 Coordinates: 527d12_Contig309G 35133-35454
gtgttcatgcag**GTCAGGAGCGGGTCGTGATTGCCGACGATCTCCCGCACCCGT**
TCGGTCTGACGCAGTACAGCGATTATATCTACTGGACAGACTGGAATCT
GCACAGCATTGAGCGGGCCGACAAGACTAGCGGCCGGAACCGCACCCTC
ATCCAGGGCCACCTGGACTTCGTGATGGACATCCTGGTGTTCCACTCCT
CCCGCCAGGATGGCCTCAATGACTGTATGCACAACAACGGGCAGTGTGG
GCAGCTGTGCCTTGCCATCCCCGGCGGCCACCGCTGCGGCTGCGCCTCA
CACTACACCCTGGACCCCAGCAGCCGCAACTGCAGCCgtaagtgcctcatggt

.......2006 nt......

Exon 13 Coordinates: 527d12_Contig309G 37460-37659
gcctcctcta**CGCCCACCACCTTCTTGCTGTTCAGCCAGAAATCTGCCATCAGT**
CGGATGATCCCGGACGACCAGCACAGCCCGGATCTCATCCTGCCCCTGC
ATGGACTGAGGAACGTCAAAGCCATCGACTATGACCCACTGGACAAGTT
CATCTACTGGGTGGATGGGCGCCAGAACATCAAGCGAGCCAAGGACGAC
GGGACCCAGgcaggtgccctgtgg

......6965 nt......

FIG. 3C

Exon 14 Coordinates: 527d12_Contig309G 44624-44832
ctttgtcttacag**CCCTTTGTTTTGACCTCTCTGAGCCAAGGCCAAAACCCAGACA**
GGCAGCCCCACGACCTCAGCATCGACATCTACAGCCGGACACTGTTCTG
GACGTGCGAGGCCACCAATACCATCAACGTCCACAGGCTGAGCGGGGAA
GCCATGGGGGTGGTGCTGCGTGGGACCGCGACAAGCCCAGGGCCATC
GTCGTCAACGCGGAGCGAGGgtaggaggccaac

……1404 nt…..

Exon 15 Coordinates: 527d12_Contig309G 46236-46427
ccaccctcccgcag**GTACCTGTACTTCACCAACATGCAGGACCGGGCAGCCAAGA**
TCGAACGCGCAGCCCTGGACGGCACCGAGCGCGAGGTCCTCTTCACCAC
CGGCCTCATCCGCCCTGTGGCCCTGGTGGTGGACAACACACTGGGCAAG
CTGTTCTGGGTGGACGCGGACCTGAAGCGCATTGAGAGCTGTGACCTGT
CAGgtacgcgccccgg

…..686 nt…..

Exon 16 Coordinates: 527d12_Contig309G 47113-47322
ggctgcttgcag**GGGCCAACCGCCTGACCCTGGAGGACGCCAACATCGTGCAGC**
CTCTGGGCCTGACCATCCTTGGCAAGCATCTCTACTGGATCGACCGCCA
GCAGCAGATGATCGAGCGTGTGGAGAAGACCACCGGGGACAAGCGGAC
TCGCATCCAGGGCCGTGTCGCCCACCTCACTGGCATCCATGCAGTGGAG
GAAGTCAGCCTGGAGGAGTTCTgtacgtgggggc

…..3884 nt……

Exon 17 Coordinates: 527d12_Contig309G 51206-51331
ttgtctttgcag**CAGCCCACCCATGTGCCCGTGACAATGGTGGCTGCTCCCACAT**
CTGTATTGCCAAGGGTGATGGGACACCACGGTGCTCATGCCCAGTCCAC
CTCGTGCTCCTGCAGAACCTGCTGACCTGTGGAGgtaggtgtgacctaggtgc

….3905 nt…….

Exon 18 Coordinates: 527d12_Contig309G 55236-55472
gttctcctctgtccctcccccag**AGCCGCCCACCTGCTCCCCGGACCAGTTTGCATGTG**
CCACAGGGGAGATCGACTGTATCCCCGGGGCCTGGCGCTGTGACGGCTT
TCCCGAGTGCGATGACCAGAGCGACGAGGAGGGCTGCCCCGTGTGCTCC
GCCGCCCAGTTCCCCTGCGCGCGGGGTCAGTGTGTGGACCTGCGCCTGC
GCTGCGACGGCGAGGCAGACTGTCAGGACCGCTCAGACGAGGTGGACT
GTGACGgtgaggccctcc

…….3052 nt…..

FIG. 3D

Exon 19 Coordinates: 527d12_Contig309G 58524-58634
tctccttgcag**CCATCTGCCTGCCCAACCAGTTCCGGTGTGCGAGCGGCCAGTGTGTCCTCATCAAACAGCAGTGCGACTCCTTCCCCGACTGTATCGACGGCTCCGACGAGCTCATGTGTG**gtgagccagctt

........1448 nt......

Exon 20 Coordinates: 527d12_Contig309G 60082-60319
gtttgtctctggcag**AAATCACCAAGCCGCCCTCAGACGACAGCCCGGCCCACAGCAGTGCCATCGGGCCCGTCATTGGCATCATCCTCTCTCTCTTCGTCATGGGTGGTGTCTATTTTGTGTGCCAGCGCGTGGTGTGCCAGCGCTATGCGGGGGCCAACGGGCCCTTCCCGCACGAGTATGTCAGCGGGACCCCGCACGTGCCCCTCAATTTCATAGCCCCGGGCGGTTCCCAGCATGGCCCCTTCACAG**gtaaggagcctgagatatggaa

....1095 nt.....

Exon 21 Coordinates: 527d12_Contig309G 61414-61552
cttccctgccag**GCATCGCATGCGGAAAGTCCATGATGAGCTCCGTGAGCCTGATGGGGGGCCGGGGCGGGGTGCCCCTCTACGACCGGAACCACGTCACAGGGGCCTCGTCCAGCAGCTCGTCCAGCACGAAGGCCACGCTGTACCCGCCG**gtgaggggcggg

......6513 nt......

Exon 22 Coordinates: 527d12_Contig309G 68065-68162
ttggctctcctcag**ATCCTGAACCCGCCGCCCTCCCCGGCCACGGACCCCTCCCTGTACAACATGGACATGTTCTACTCTTCAAACATTCCGGCCACTGCGAGACCGTACAG**gtaggacatcccctgcag

.......2273 nt.....

FIG. 3E

Exon 23 Coordinates: 527d12_Contig309G 70435-70901
tcaaacattccggccactgcgagaccgtacag**GCCCTACATCATTCGAGGAATGGCGCCCCC**
GACGACGCCCTGCAGCACCGACGTGTGTGACAGCGACTACAGCGCCAGC
CGCTGGAAGGCCAGCAAGTACTACCTGGATTTGAACTCGGACTCAGACC
CCTATCCACCCCCACCCACGCCCCACAGCCAGTACCTGTCGGCGGAGGA
CAGCTGCCCGCCCTCGCCCGCCACCGAGAGGAGCTACTTCCATCTCTTC
CCGCCCCCTCCGTCCCCCTGCACGGACTCATCCTGACCTCGGCCGGGCCA
CTCTGGCTTCTCTGTGCCCCTGTAAATAGTTTTAAATATGAACAAAGAAAAAA
ATATATTTTATGATTTAAAAAATAAATATAATTGGGATTTTAAAAACATGAGA
AATGTGAACTGTGATGGGGTGGGCAGGGCTGGGAGAACTTTGTACAGTGGAG
AAATATTTATAAACTTAATTTTGTAAAACA

FIG. 3F

Model for a LDL Receptor-Related protein, Zmax1

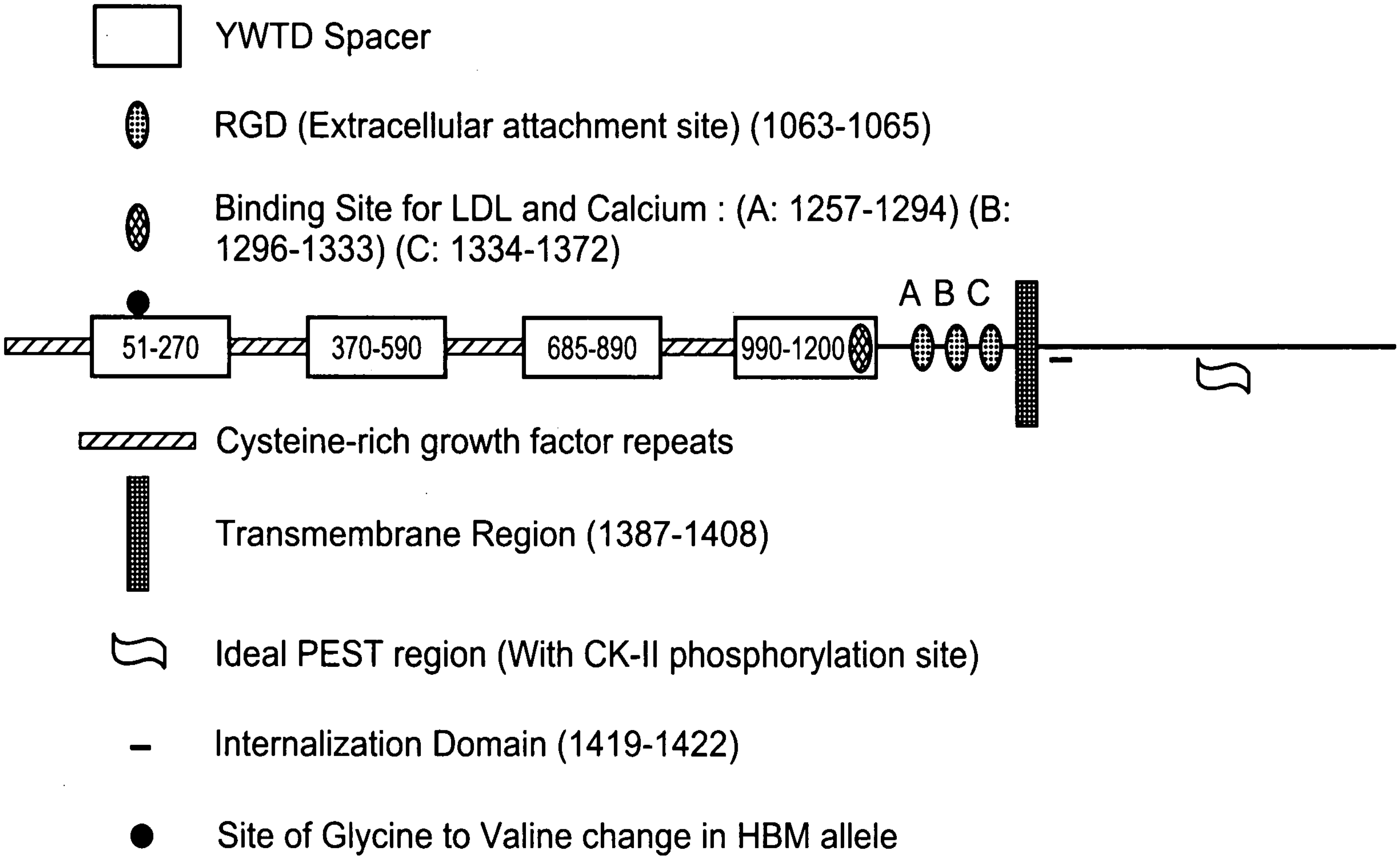

YWTD Spacer
RGD (Extracellular attachment site) (1063-1065)
Binding Site for LDL and Calcium : (A: 1257-1294) (B: 1296-1333) (C: 1334-1372)
51-270
370-590
685-890
990-1200
A B C
Cysteine-rich growth factor repeats
Transmembrane Region (1387-1408)
Ideal PEST region (With CK-II phosphorylation site)
Internalization Domain (1419-1422)
Site of Glycine to Valine change in HBM allele

FIG. 4

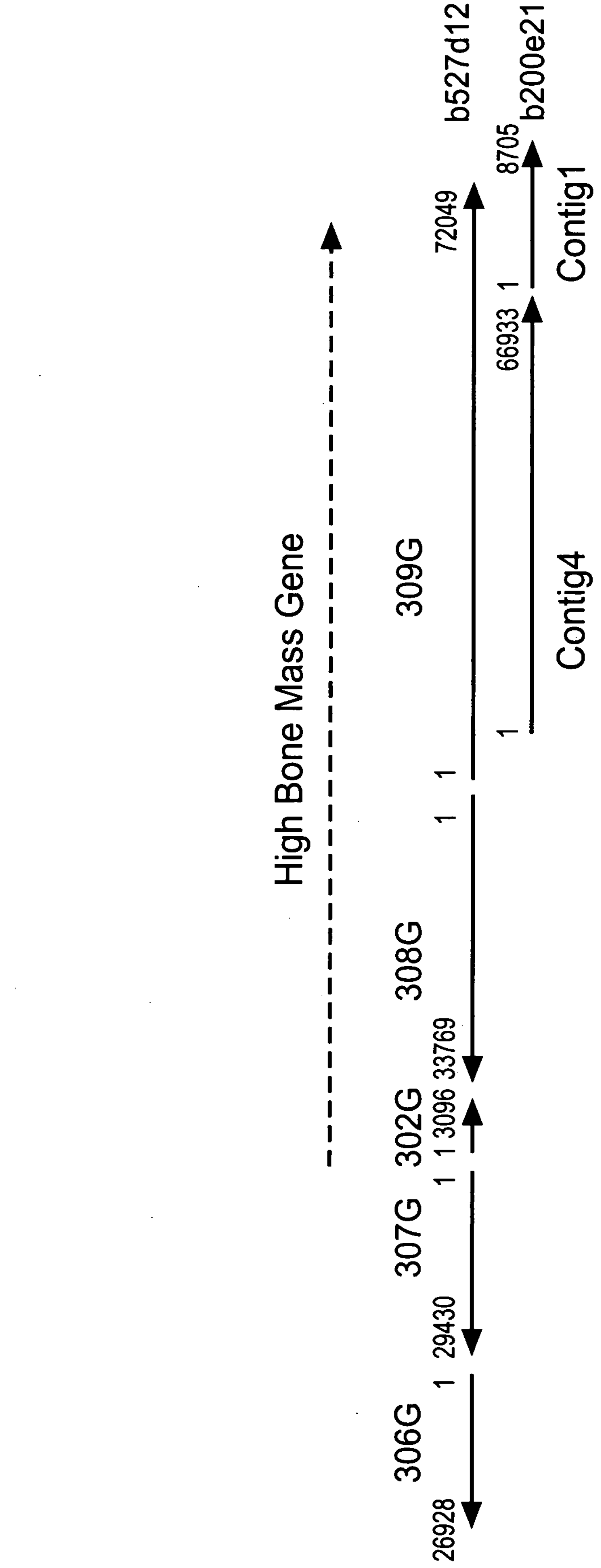

High Bone Mass Gene
26928
306G
1
29430
307G
1
1
302G
3096
33769
308G
1
1
309G
72049
b527d12
1
Contig4
66933
1
Contig1
8705
b200e21

FIG. 5

FIG. 6A

```
  1  ACTAAAGCGCCGCCGCCGCGCCATGGAGCCCGAGTGAGCGCGGCGCGGGCCCGTCCGGCC   60
 61  GCCGGACAACATGGAGGCAGCGCCGCCCGGGCCGCCGTGGCCGCTGCTGCTGCTGCTGCT  120
  1            M  E  A  A  P  P  G  P  P  W  P  L  L  L  L  L   17

121  GCTGCTGCTGGCGCTGTGCGGCTGCCCGGCCCCCGCCGCGGCCTCGCCGCTCCTGCTATT  180
 18   L  L  L  A  L  C  G  C  P  A  P  A  A  A  S  P  L  L  L  F   37

181  TGCCAACCGCCGGGACGTACGGCTGGTGGACGCCGGCGGAGTCAAGCTGGAGTCCACCAT  240
 38   A  N  R  R  D  V  R  L  V  D  A  G  G  V  K  L  E  S  T  I   57

241  CGTGGTCAGCGGCCTGGAGGATGCGGCCGCAGTGGACTTCCAGTTTTCCAAGGGAGCCGT  300
 58   V  V  S  G  L  E  D  A  A  A  V  D  F  Q  F  S  K  G  A  V   77

301  GTACTGGACAGACGTGAGCGAGGAGGCCATCAAGCAGACCTACCTGAACCAGACGGGGGC  360
 78   Y  W  T  D  V  S  E  E  A  I  K  Q  T  Y  L  N  Q  T  G  A   97

361  CGCCGTGCAGAACGTGGTCATCTCCGGCCTGGTCTCTCCCGACGGCCTCGCCTGCGACTG  420
 98   A  V  Q  N  V  V  I  S  G  L  V  S  P  D  G  L  A  C  D  W  117

421  GGTGGGCAAGAAGCTGTACTGGACGGACTCAGAGACCAACCGCATCGAGGTGGCCAACCT  480
118   V  G  K  K  L  Y  W  T  D  S  E  T  N  R  I  E  V  A  N  L  137

481  CAATGGCACATCCCGGAAGGTGCTCTTCTGGCAGGACCTTGACCAGCCGAGGGCCATCGC  540
138   N  G  T  S  R  K  V  L  F  W  Q  D  L  D  Q  P  R  A  I  A  157

541  CTTGGACCCCGCTCACGGGTACATGTACTGGACAGACTGGGGTGAGACGCCCCGGATTGA  600
158   L  D  P  A  H  G  Y  M  Y  W  T  D  W  G  E  T  P  R  I  E  177
```

FIG. 6B

```
 601  GCGGGCAGGGATGGATGGCAGCACCCGGAAGATCATTGTGGACTCGGACATTTACTGGCC   660
 178   R  A  G  M  D  G  S  T  R  K  I  I  V  D  S  D  I  Y  W  P   197

 661  CAATGGACTGACCATCGACCTGGAGGAGCAGAAGCTCTACTGGGCTGACGCCAAGCTCAG   720
 198   N  G  L  T  I  D  L  E  E  Q  K  L  Y  W  A  D  A  K  L  S   217

 721  CTTCATCCACCGTGCCAACCTGGACGGCTCGTTCCGGCAGAAGGTGGTGGAGGGCAGCCT   780
 218   F  I  H  R  A  N  L  D  G  S  F  R  Q  K  V  V  E  G  S  L   237

 781  GACGCACCCCTTCGCCCTGACGCTCTCCGGGGACACTCTGTACTGGACAGACTGGCAGAC   840
 238   T  H  P  F  A  L  T  L  S  G  D  T  L  Y  W  T  D  W  Q  T   257

 841  CCGCTCCATCCATGCCTGCAACAAGCGCACTGGGGGGAAGAGGAAGGAGATCCTGAGTGC   900
 258   R  S  I  H  A  C  N  K  R  T  G  G  K  R  K  E  I  L  S  A   277

 901  CCTCTACTCACCCATGGACATCCAGGTGCTGAGCCAGGAGCGGCAGCCTTTCTTCCACAC   960
 278   L  Y  S  P  M  D  I  Q  V  L  S  Q  E  R  Q  P  F  F  H  T   297

 961  TCGCTGTGAGGAGGACAATGGCGGCTGCTCCCACCTGTGCCTGCTGTCCCCAAGCGAGCC   1020
 298   R  C  E  E  D  N  G  G  C  S  H  L  C  L  L  S  P  S  E  P   317

1021  TTTCTACACATGCGCCTGCCCCACGGGTGTGCAGCTGCAGGACAACGGCAGGACGTGTAA   1080
 318   F  Y  T  C  A  C  P  T  G  V  Q  L  Q  D  N  G  R  T  C  K   337

1081  GGCAGGAGCCGAGGAGGTGCTGCTGCTGGCCCGGCGGACGGACCTACGGAGGATCTCGCT   1140
 338   A  G  A  E  E  V  L  L  L  A  R  R  T  D  L  R  R  I  S  L   357
```

FIG. 6C

```
1141  GGACACGCCGGACTTCACCGACATCGTGCTGCAGGTGGACGACATCCGGCACGCCATTGC  1200
 358   D  T  P  D  F  T  D  I  V  L  Q  V  D  D  I  R  H  A  I  A   377

1201  CATCGACTACGACCCGCTAGAGGGCTATGTCTACTGGACAGATGACGAGGTGCGGGCCAT  1260
 378   I  D  Y  D  P  L  E  G  Y  V  Y  W  T  D  D  E  V  R  A  I   397

1261  CCGCAGGGCGTACCTGGACGGGTCTGGGGCGCAGACGCTGGTCAACACCGAGATCAACGA  1320
 398   R  R  A  Y  L  D  G  S  G  A  Q  T  L  V  N  T  E  I  N  D   417

1321  CCCCGATGGCATCGCGGTCGACTGGGTGGCCCGAAACCTCTACTGGACCGACACGGGCAC  1380
 418   P  D  G  I  A  V  D  W  V  A  R  N  L  Y  W  T  D  T  G  T   437

1381  GGACCGCATCGAGGTGACGCGCCTCAACGGCACCTCCCGCAAGATCCTGGTGTCGGAGGA  1440
 438   D  R  I  E  V  T  R  L  N  G  T  S  R  K  I  L  V  S  E  D   457

1441  CCTGGACGAGCCCCGAGCCATCGCACTGCACCCCGTGATGGGCCTCATGTACTGGACAGA  1500
 458   L  D  E  P  R  A  I  A  L  H  P  V  M  G  L  M  Y  W  T  D   477

1501  CTGGGGAGAGAACCCTAAAATCGAGTGTGCCAACTTGGATGGGCAGGAGCGGCGTGTGCT  1560
 478   W  G  E  N  P  K  I  E  C  A  N  L  D  G  Q  E  R  R  V  L   497

1561  GGTCAATGCCTCCCTCGGGTGGCCCAACGGCCTGGCCCTGGACCTGCAGGAGGGGAAGCT  1620
 498   V  N  A  S  L  G  W  P  N  G  L  A  L  D  L  Q  E  G  K  L   517

1621  CTACTGGGGAGACGCCAAGACAGACAAGATCGAGGTGATCAATGTTGATGGGACGAAGAG  1680
 518   Y  W  G  D  A  K  T  D  K  I  E  V  I  N  V  D  G  T  K  R   537
```

FIG. 6D

```
1681  GCGGACCCTCCTGGAGGACAAGCTCCCGCACATTTTCGGGTTCACGCTGCTGGGGACTT  1740
 538   R  T  L  L  E  D  K  L  P  H  I  F  G  F  T  L  L  G  D  F   557

1741  CATCTACTGGACTGACTGGCAGCGCCGCAGCATCGAGCGGGTGCACAAGGTCAAGGCCAG  1800
 558   I  Y  W  T  D  W  Q  R  R  S  I  E  R  V  H  K  V  K  A  S   577

1801  CCGGGACGTCATCATTGACCAGCTGCCCGACCTGATGGGGCTCAAAGCTGTGAATGTGGC  1860
 578   R  D  V  I  I  D  Q  L  P  D  L  M  G  L  K  A  V  N  V  A   597

1861  CAAGGTCGTCGGAACCAACCCGTGTGCGGACAGGAACGGGGGGTGCAGCCACCTGTGCTT  1920
 598   K  V  V  G  T  N  P  C  A  D  R  N  G  G  C  S  H  L  C  F   617

1921  CTTCACACCCCACGCAACCCGGTGTGGCTGCCCCATCGGCCTGGAGCTGCTGAGTGACAT  1980
 618   F  T  P  H  A  T  R  C  G  C  P  I  G  L  E  L  L  S  D  M   637

1981  GAAGACCTGCATCGTGCCTGAGGCCTTCTTGGTCTTCACCAGCAGAGCCGCCATCCACAG  2040
 638   K  T  C  I  V  P  E  A  F  L  V  F  T  S  R  A  A  I  H  R   657

2041  GATCTCCCTCGAGACCAATAACAACGACGTGGCCATCCCGCTCACGGGCGTCAAGGAGGC  2100
 658   I  S  L  E  T  N  N  N  D  V  A  I  P  L  T  G  V  K  E  A   677

2101  CTCAGCCCTGGACTTTGATGTGTCCAACAACCACATCTACTGGACAGACGTCAGCCTGAA  2160
 678   S  A  L  D  F  D  V  S  N  N  H  I  Y  W  T  D  V  S  L  K   697

2161  GACCATCAGCCGCGCCTTCATGAACGGGAGCTCGGTGGAGCACGTGGTGGAGTTTGGCCT  2220
 698   T  I  S  R  A  F  M  N  G  S  S  V  E  H  V  V  E  F  G  L   717
```

FIG. 6E

```
2221  TGACTACCCCGAGGGCATGGCCGTTGACTGGATGGGCAAGAACCTCTACTGGGCCGACAC  2280
 718   D  Y  P  E  G  M  A  V  D  W  M  G  K  N  L  Y  W  A  D  T   737

2281  TGGGACCAACAGAATCGAAGTGGCGCGGCTGGACGGGCAGTTCCGGCAAGTCCTCGTGTG  2340
 738   G  T  N  R  I  E  V  A  R  L  D  G  Q  F  R  Q  V  L  V  W   757

2341  GAGGGACTTGGACAACCCGAGGTCGCTGGCCCTGGATCCCACCAAGGGCTACATCTACTG  2400
 758   R  D  L  D  N  P  R  S  L  A  L  D  P  T  K  G  Y  I  Y  W   777

2401  GACCGAGTGGGGCGGCAAGCCGAGGATCGTGCGGGCCTTCATGGACGGGACCAACTGCAT  2460
 778   T  E  W  G  G  K  P  R  I  V  R  A  F  M  D  G  T  N  C  M   797

2461  GACGCTGGTGGACAAGGTGGGCCGGGCCAACGACCTCACCATTGACTACGCTGACCAGCG  2520
 798   T  L  V  D  K  V  G  R  A  N  D  L  T  I  D  Y  A  D  Q  R   817

2521  CCTCTACTGGACCGACCTGGACACCAACATGATCGAGTCGTCCAACATGCTGGGTCAGGA  2580
 818   L  Y  W  T  D  L  D  T  N  M  I  E  S  S  N  M  L  G  Q  E   837

2581  GCGGGTCGTGATTGCCGACGATCTCCCGCACCCGTTCGGTCTGACGCAGTACAGCGATTA  2640
 838   R  V  V  I  A  D  D  L  P  H  P  F  G  L  T  Q  Y  S  D  Y   857

2641  TATCTACTGGACAGACTGGAATCTGCACAGCATTGAGCGGGCCGACAAGACTAGCGGCCG  2700
 858   I  Y  W  T  D  W  N  L  H  S  I  E  R  A  D  K  T  S  G  R   877

2701  GAACCGCACCCTCATCCAGGGCCACCTGGACTTCGTGATGGACATCCTGGTGTTCCACTC  2760
 878   N  R  T  L  I  Q  G  H  L  D  F  V  M  D  I  L  V  F  H  S   897
```

FIG. 6F

```
2761  CTCCCGCCAGGATGGCCTCAATGACTGTATGCACAACAACGGGCAGTGTGGGCAGCTGTG  2820
 898   S  R  Q  D  G  L  N  D  C  M  H  N  N  G  Q  C  G  Q  L  C   917

2821  CCTTGCCATCCCCGGCGGCCACCGCTGCGGCTGCGCCTCACACTACACCCTGGACCCCAG  2880
 918   L  A  I  P  G  G  H  R  C  G  C  A  S  H  Y  T  L  D  P  S   937

2881  CAGCCGCAACTGCAGCCCGCCCACCACCTTCTTGCTGTTCAGCCAGAAATCTGCCATCAG  2940
 938   S  R  N  C  S  P  P  T  T  F  L  L  F  S  Q  K  S  A  I  S   957

2941  TCGGATGATCCCGGACGACCAGCACAGCCCGGATCTCATCCTGCCCCTGCATGGACTGAG  3000
 958   R  M  I  P  D  D  Q  H  S  P  D  L  I  L  P  L  H  G  L  R   977

3001  GAACGTCAAAGCCATCGACTATGACCCACTGGACAAGTTCATCTACTGGGTGGATGGGCG  3060
 978   N  V  K  A  I  D  Y  D  P  L  D  K  F  I  Y  W  V  D  G  R   997

3061  CCAGAACATCAAGCGAGCCAAGGACGACGGGACCCAGCCCTTTGTTTTGACCTCTCTGAG  3120
 998   Q  N  I  K  R  A  K  D  D  G  T  Q  P  F  V  L  T  S  L  S  1017

3121  CCAAGGCCAAAACCCAGACAGGCAGCCCCACGACCTCAGCATCGACATCTACAGCCGGAC  3180
1018   Q  G  Q  N  P  D  R  Q  P  H  D  L  S  I  D  I  Y  S  R  T  1037

3181  ACTGTTCTGGACGTGCGAGGCCACCAATACCATCAACGTCCACAGGCTGAGCGGGGAAGC  3240
1038   L  F  W  T  C  E  A  T  N  T  I  N  V  H  R  L  S  G  E  A  1057

3241  CATGGGGGTGGTGCTGCGTGGGGACCGCGACAAGCCCAGGGCCATCGTCGTCAACGCGGA  3300
1058   M  G  V  V  L  R  G  D  R  D  K  P  R  A  I  V  V  N  A  E  1077
```

FIG. 6G

```
3301  GCGAGGGTACCTGTACTTCACCAACATGCAGGACCGGGCAGCCAAGATCGAACGCGCAGC  3360
1078   R  G  Y  L  Y  F  T  N  M  Q  D  R  A  A  K  I  E  R  A  A   1097

3361  CCTGGACGGCACCGAGCGCGAGGTCCTCTTCACCACCGGCCTCATCCGCCCTGTGGCCCT  3420
1098   L  D  G  T  E  R  E  V  L  F  T  T  G  L  I  R  P  V  A  L   1117

3421  GGTGGTGGACAACACACTGGGCAAGCTGTTCTGGGTGGACGCGGACCTGAAGCGCATTGA  3480
1118   V  V  D  N  T  L  G  K  L  F  W  V  D  A  D  L  K  R  I  E   1137

3481  GAGCTGTGACCTGTCAGGGGCCAACCGCCTGACCCTGGAGGACGCCAACATCGTGCAGCC  3540
1138   S  C  D  L  S  G  A  N  R  L  T  L  E  D  A  N  I  V  Q  P   1157

3541  TCTGGGCCTGACCATCCTTGGCAAGCATCTCTACTGGATCGACCGCCAGCAGCAGATGAT  3600
1158   L  G  L  T  I  L  G  K  H  L  Y  W  I  D  R  Q  Q  Q  M  I   1177

3601  CGAGCGTGTGGAGAAGACCACCGGGGACAAGCGGACTCGCATCCAGGGCCGTGTCGCCCA  3660
1178   E  R  V  E  K  T  T  G  D  K  R  T  R  I  Q  G  R  V  A  H   1197

3661  CCTCACTGGCATCCATGCAGTGGAGGAAGTCAGCCTGGAGGAGTTCTCAGCCCACCCATG  3720
1198   L  T  G  I  H  A  V  E  E  V  S  L  E  E  F  S  A  H  P  C   1217

3721  TGCCCGTGACAATGGTGGCTGCTCCCACATCTGTATTGCCAAGGGTGATGGGACACCACG  3780
1218   A  R  D  N  G  G  C  S  H  I  C  I  A  K  G  D  G  T  P  R   1237

3781  GTGCTCATGCCCAGTCCACCTCGTGCTCCTGCAGAACCTGCTGACCTGTGGAGAGCCGCC  3840
1238   C  S  C  P  V  H  L  V  L  L  Q  N  L  L  T  C  G  E  P  P   1257
```

FIG. 6H

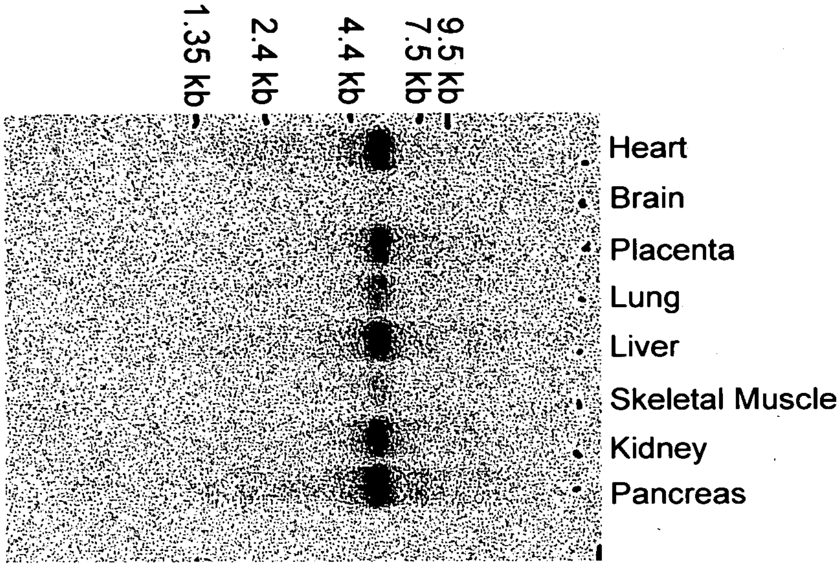
```
3841  CACCTGCTCCCCGGACCAGTTTGCATGTGCCACAGGGGAGATCGACTGTATCCCCGGGGC  3900
1258   T  C  S  P  D  Q  F  A  C  A  T  G  E  I  D  C  I  P  G  A   1277

3901  CTGGCGCTGTGACGGCTTTCCCGAGTGCGATGACCAGAGCGACGAGGAGGGCTGCCCCGT  3960
1278   W  R  C  D  G  F  P  E  C  D  D  Q  S  D  E  E  G  C  P  V   1297

3961  GTGCTCCGCCGCCCAGTTCCCCTGCGCGCGGGGTCAGTGTGTGGACCTGCGCCTGCGCTG  4020
1298   C  S  A  A  Q  F  P  C  A  R  G  Q  C  V  D  L  R  L  R  C   1317

4021  CGACGGCGAGGCAGACTGTCAGGACCGCTCAGACGAGGTGGACTGTGACGCCATCTGCCT  4080
1318   D  G  E  A  D  C  Q  D  R  S  D  E  V  D  C  D  A  I  C  L   1337

4081  GCCCAACCAGTTCCGGTGTGCGAGCGGCCAGTGTGTCCTCATCAAACAGCAGTGCGACTC  4140
1338   P  N  Q  F  R  C  A  S  G  Q  C  V  L  I  K  Q  Q  C  D  S   1357

4141  CTTCCCCGACTGTATCGACGGCTCCGACGAGCTCATGTGTGAAATCACCAAGCCGCCCTC  4200
1358   F  P  D  C  I  D  G  S  D  E  L  M  C  E  I  T  K  P  P  S   1377

4201  AGACGACAGCCCGGCCCACAGCAGTGCCATCGGGCCCGTCATTGGCATCATCCTCTCTCT  4260
1378   D  D  S  P  A  H  S  S  A  I  G  P  V  I  G  I  I  L  S  L   1397

4261  CTTCGTCATGGGTGGTGTCTATTTTGTGTGCCAGCGCGTGGTGTGCCAGCGCTATGCGGG  4320
1398   F  V  M  G  G  V  Y  F  V  C  Q  R  V  V  C  Q  R  Y  A  G   1417

4321  GGCCAACGGGCCCTTCCCGCACGAGTATGTCAGCGGGACCCCGCACGTGCCCCTCAATTT  4380
1418   A  N  G  P  F  P  H  E  Y  V  S  G  T  P  H  V  P  L  N  F   1437
```

FIG. 6I

```
4381  CATAGCCCCGGGCGGTTCCCAGCATGGCCCCTTCACAGGCATCGCATGCGGAAAGTCCAT  4440
1438   I  A  P  G  G  S  Q  H  G  P  F  T  G  I  A  C  G  K  S  M   1457

4441  GATGAGCTCCGTGAGCCTGATGGGGGGCCGGGGCGGGGTGCCCCTCTACGACCGGAACCA  4500
1458   M  S  S  V  S  L  M  G  G  R  G  G  V  P  L  Y  D  R  N  H   1477

4501  CGTCACAGGGGCCTCGTCCAGCAGCTCGTCCAGCACGAAGGCCACGCTGTACCCGCCGAT  4560
1478   V  T  G  A  S  S  S  S  S  S  S  T  K  A  T  L  Y  P  P  I   1497

4561  CCTGAACCCGCCGCCCTCCCCGGCCACGGACCCCTCCCTGTACAACATGGACATGTTCTA  4620
1498   L  N  P  P  P  S  P  A  T  D  P  S  L  Y  N  M  D  M  F  Y   1517

4621  CTCTTCAAACATTCCGGCCACTGCGAGACCGTACAGGCCCTACATCATTCGAGGAATGGC  4680
1518   S  S  N  I  P  A  T  A  R  P  Y  R  P  Y  I  I  R  G  M  A   1537

4681  GCCCCCGACGACGCCCTGCAGCACCGACGTGTGTGACAGCGACTACAGCGCCAGCCGCTG  4740
1538   P  P  T  T  P  C  S  T  D  V  C  D  S  D  Y  S  A  S  R  W   1557

4741  GAAGGCCAGCAAGTACTACCTGGATTTGAACTCGGACTCAGACCCCTATCCACCCCCACC  4800
1558   K  A  S  K  Y  Y  L  D  L  N  S  D  S  D  P  Y  P  P  P  P   1577

4801  CACGCCCCACAGCCAGTACCTGTCGGCGGAGGACAGCTGCCCGCCCTCGCCCGCCACCGA  4860
1578   T  P  H  S  Q  Y  L  S  A  E  D  S  C  P  P  S  P  A  T  E   1597

4861  GAGGAGCTACTTCCATCTCTTCCCGCCCCCTCCGTCCCCCTGCACGGACTCATCCTGACC  4920
1598   R  S  Y  F  H  L  F  P  P  P  P  S  P  C  T  D  S  S         1615
```

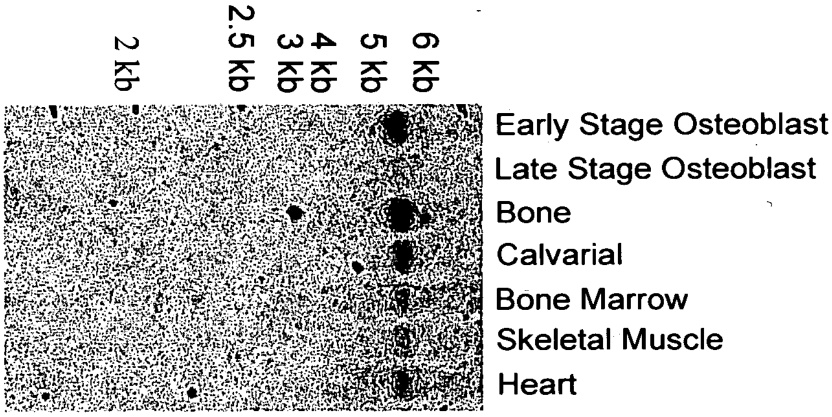
FIG. 6J

```
4921   TCGGCCGGGCCACTCTGGCTTCTCTGTGCCCCTGTAAATAGTTTTAAATATGAACAAAGA   4980
4981   AAAAAATATATTTTATGATTTAAAAAATAAATATAATTGGGATTTTAAAAACATGAGAAA   5040
5041   TGTGAACTGTGATGGGGTGGGCAGGGCTGGGAGAACTTTGTACAGTGGAGAAATATTTAT   5100
5101   AAACTTAATTTTGTAAAACA  5120
```



Northern Blot Analysis - Zmax 1

FIG. 7A



Northern Blot Analysis - Zmax 1

FIG. 7B

Zmax 1 random samples

b527d12-h_Contig087C_1.nt

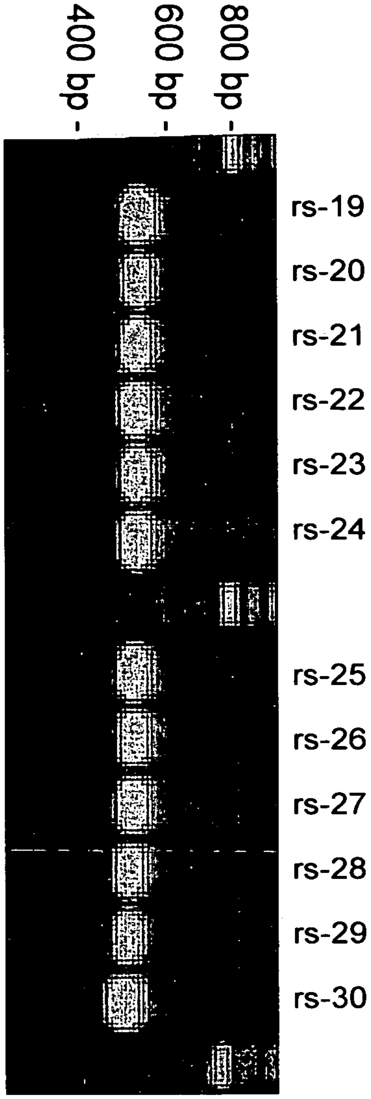


FIG. 8

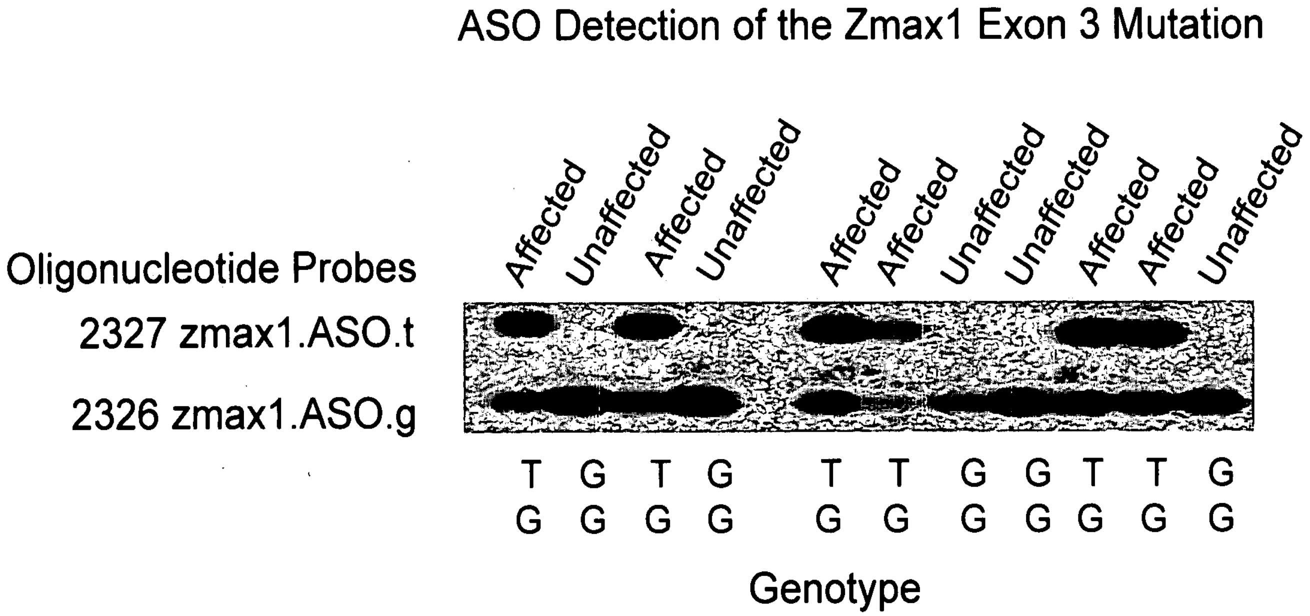

ASO Detection of the Zmax1 Exon 3 Mutation
Oligonucleotide Probes
2327 zmax1.ASO.t
2326 zmax1.ASO.g
Affected
Unaffected
Affected
Unaffected
Affected
Affected
Unaffected
Unaffected
Affected
Affected
Unaffected
T G T G T T G G T T G
G G G G G G G G G G G
Genotype

FIG. 9

Mouse Zmax1 In situ hybridization
100X Magnification

Antisense probe

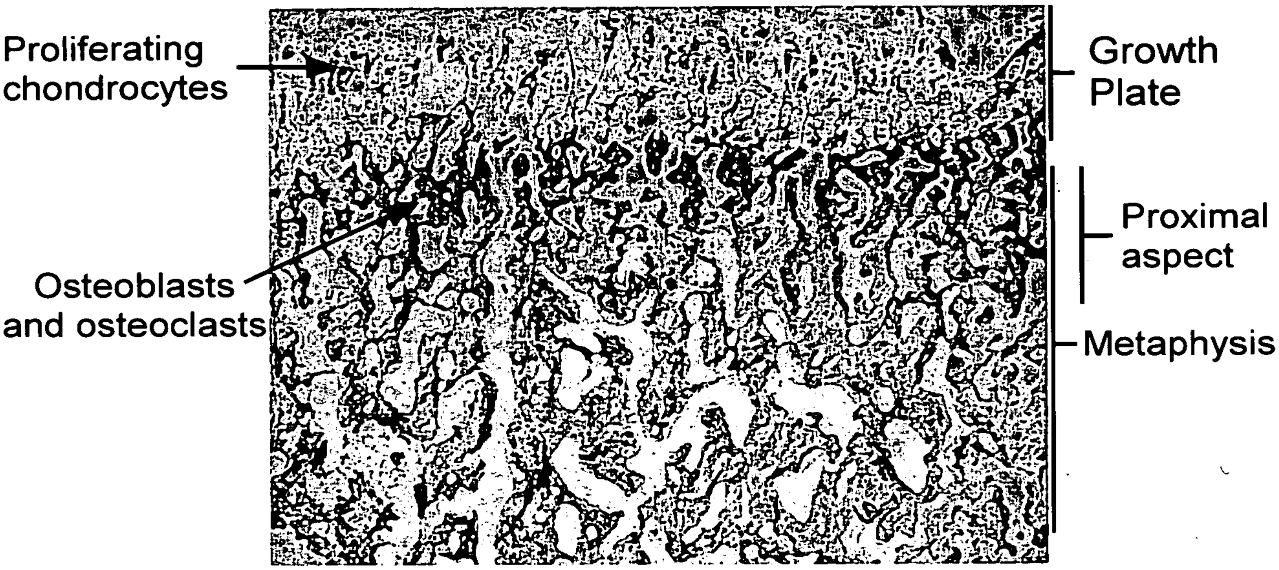


FIG. 10A

Mouse Zmax1 In situ hybridization
100X Magnification

Sense probe

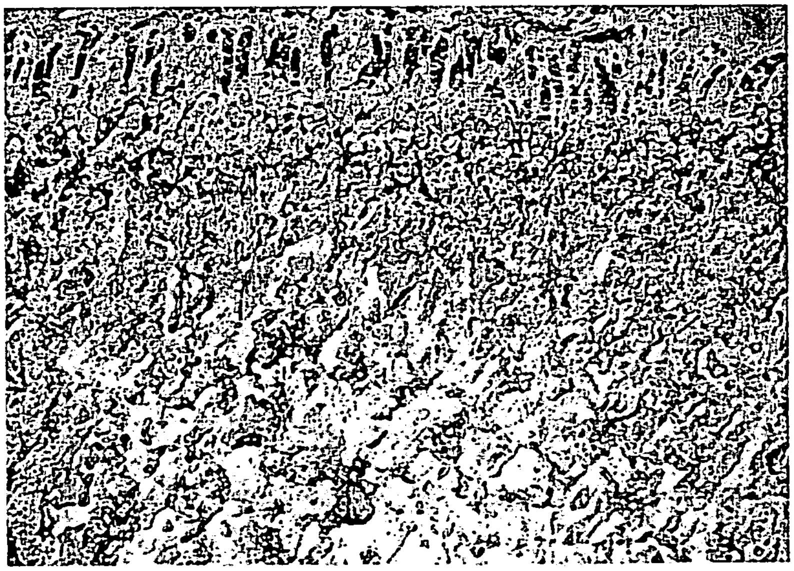
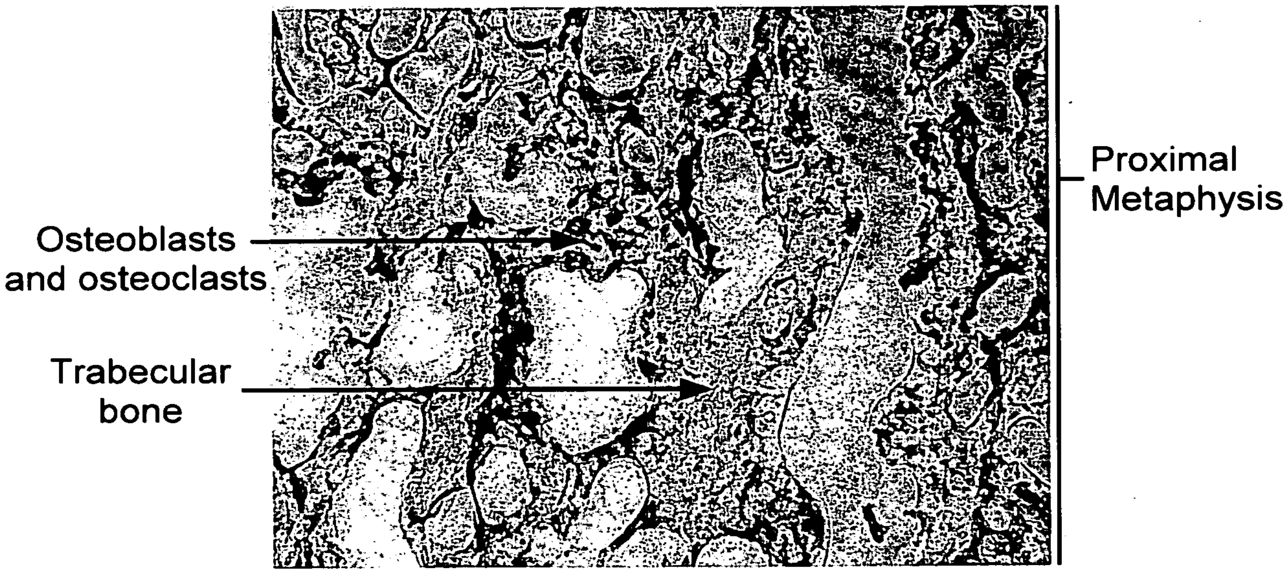
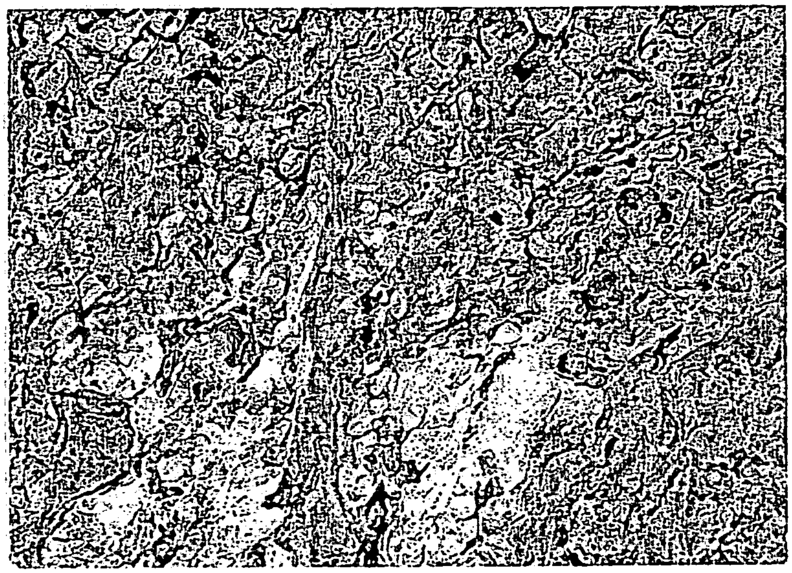


FIG. 10B



Mouse Zmax1 In situ hybridization
400X Magnification
Antisense probe

FIG. 11A



Mouse Zmax1 In situ hybridization
400X Magnification
Sense probe

FIG. 11B

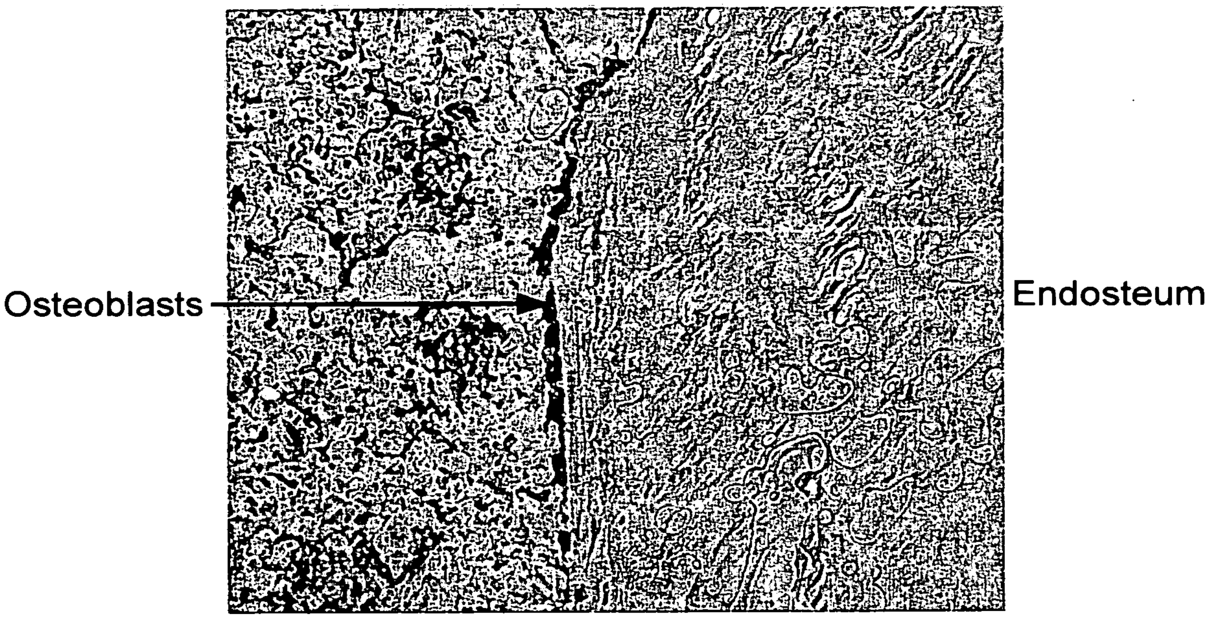

Mouse Zmax1 In situ hybridization
400X Magnification
Antisense probe

FIG. 12A

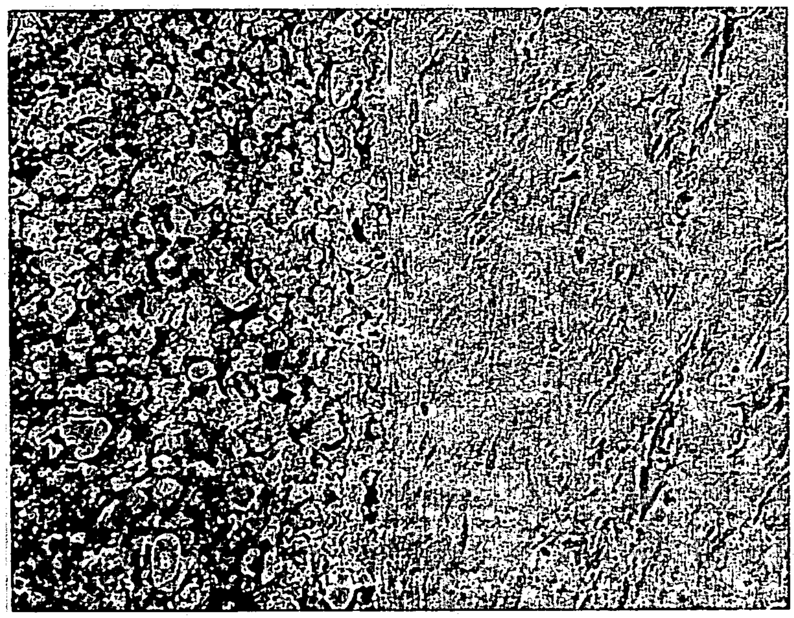

Mouse Zmax1 In situ hybridization
400X Magnification
Sense probe

FIG. 12B

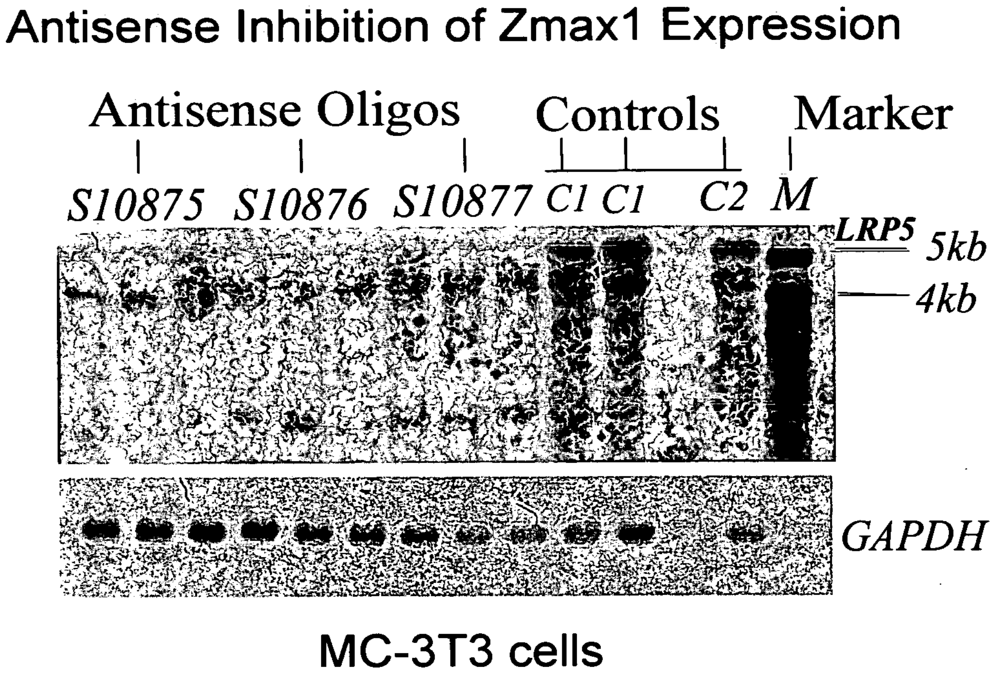

Antisense Inhibition of Zmax1 Expression
Antisense Oligos
Controls
Marker
S10875
S10876
S10877
C1
C1
C2
M
LRP5
5kb
4kb
GAPDH
MC-3T3 cells

FIG. 13

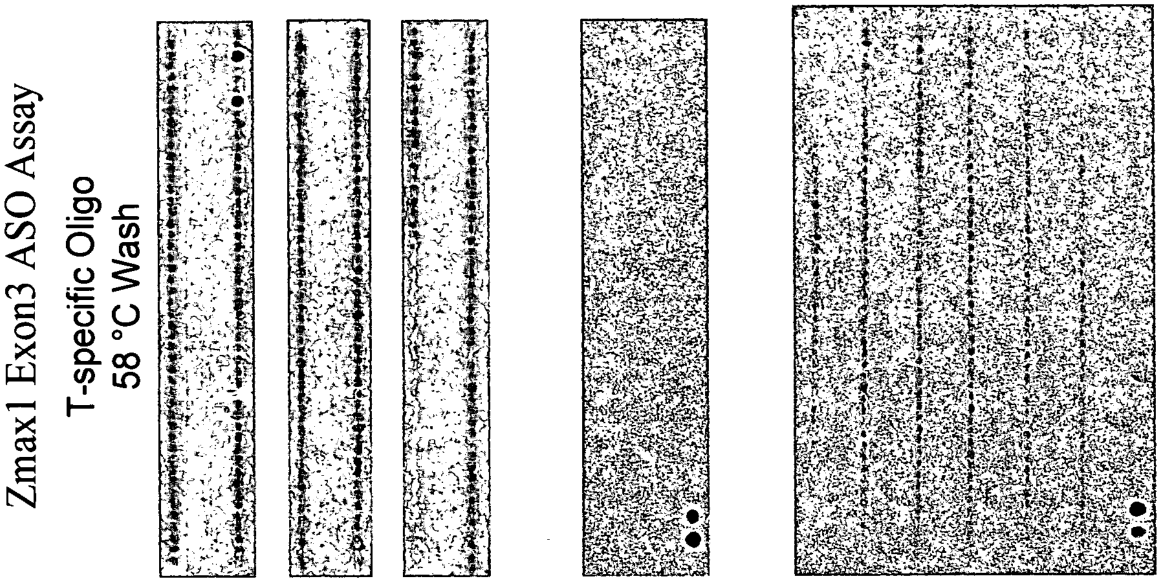


FIG. 14B

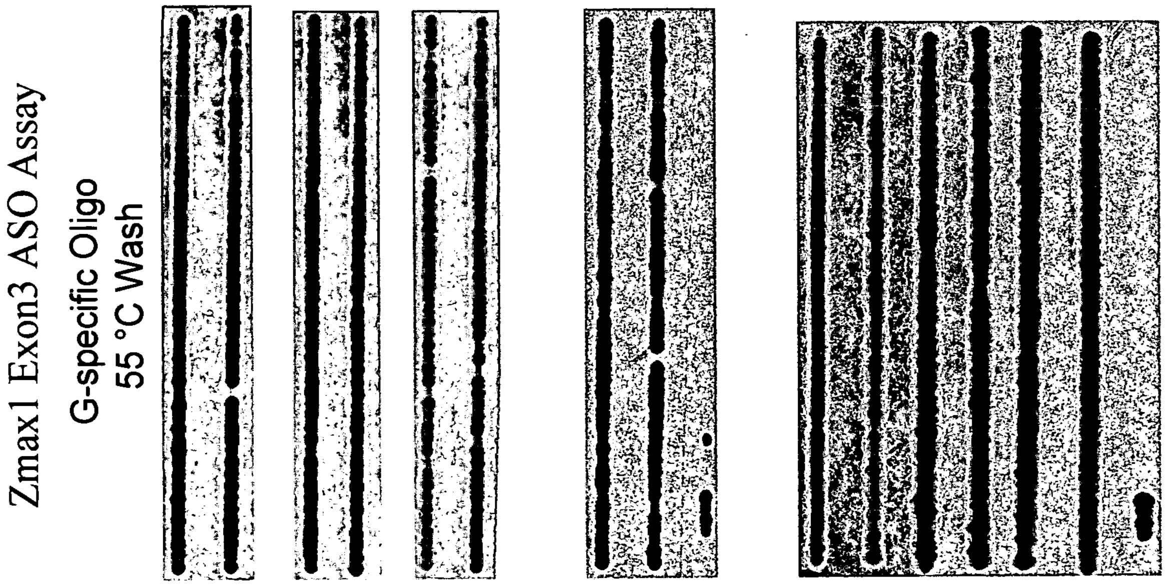


FIG. 14A

Possible Involvement of Zmax1 in Focal Adhesion Signaling

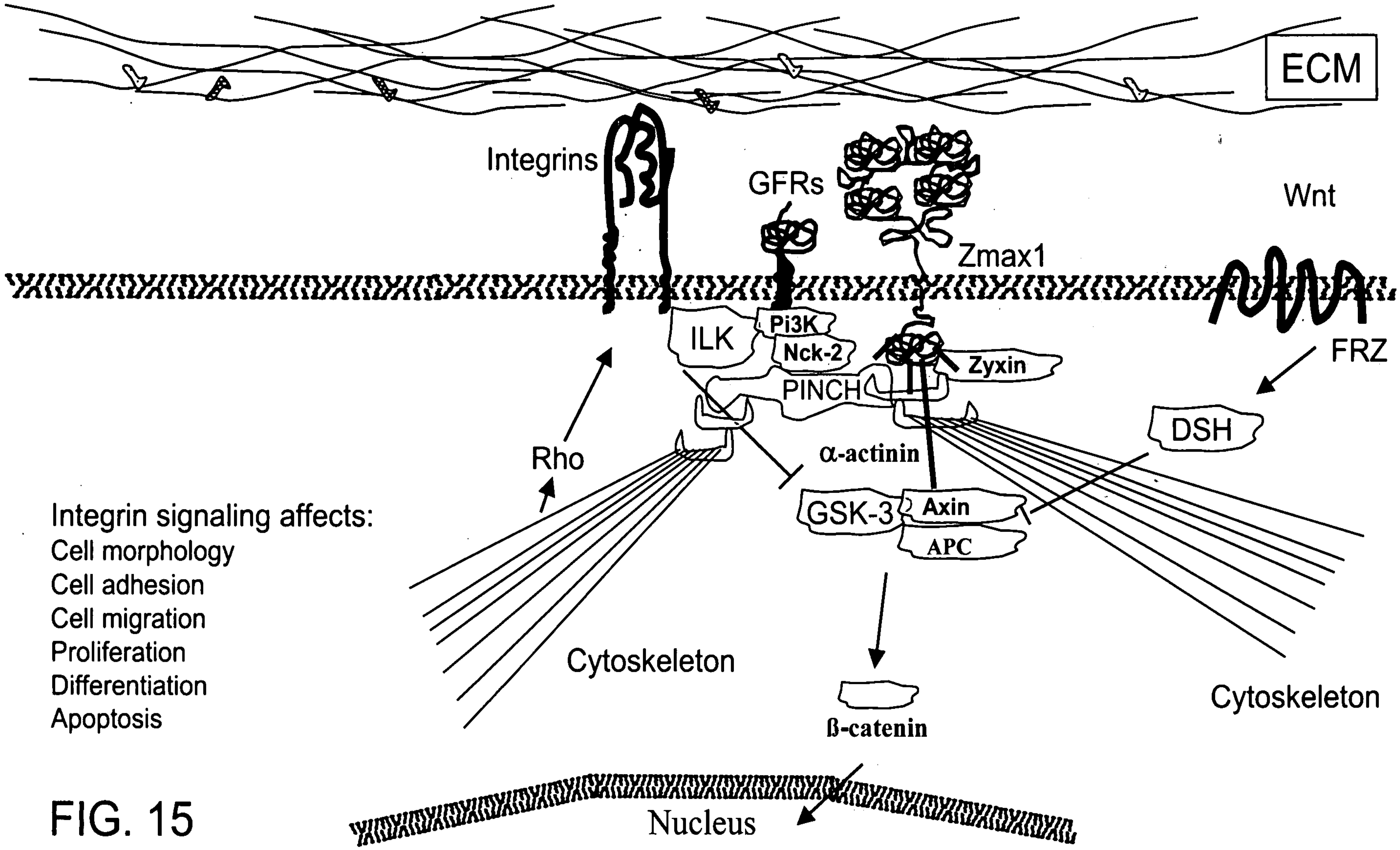


FIG. 15

ZMAX Gene Targeting Knock-in / Knock-out vectors

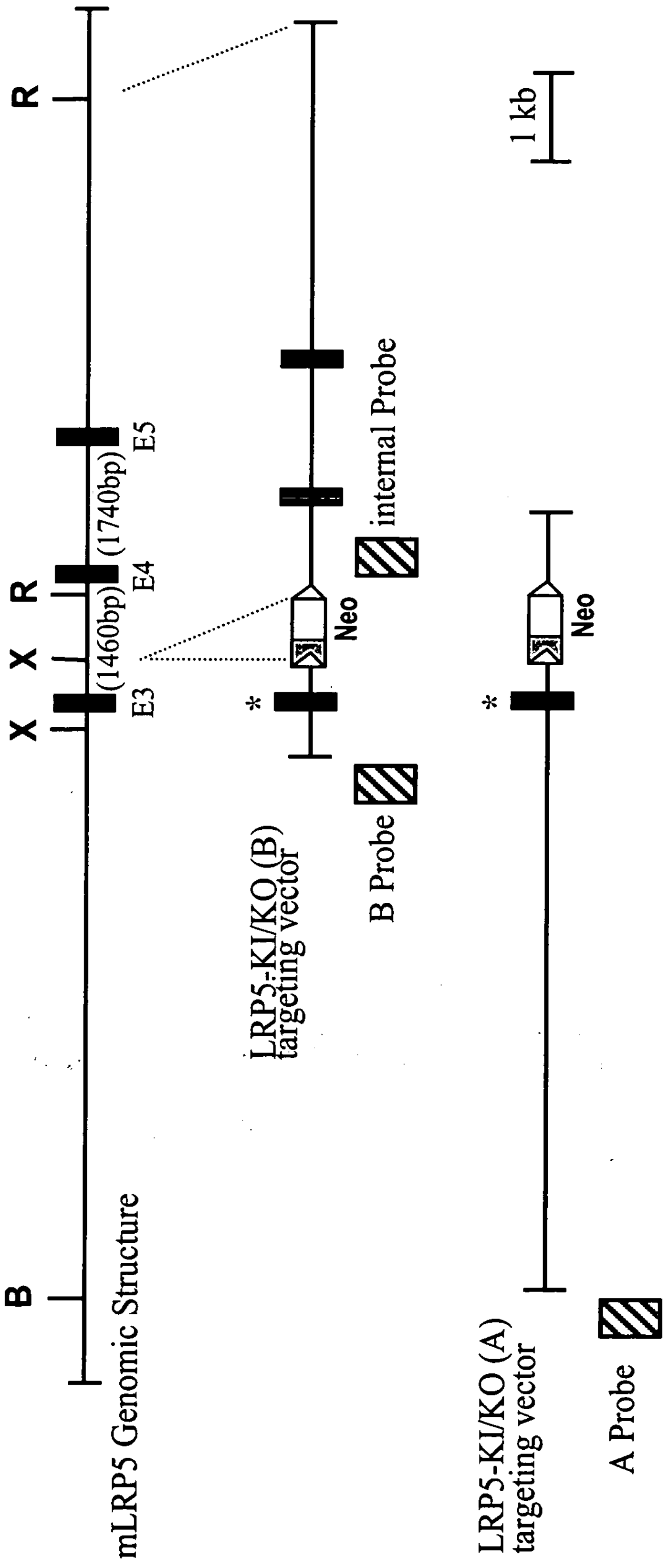


FIG. 16

HBM: Constructs for transgenic mice

Confirmation of expression

*Transient transfection into HOB-02-02 cells**

CMV βActin		Type I collagen	
HBM	Zmax1	HBM	Zmax1
X 1,000	X 1,000	X 10	X 10

**Fold increase compared to Zmax1 in cells transfected with empty vector*

FIG. 17

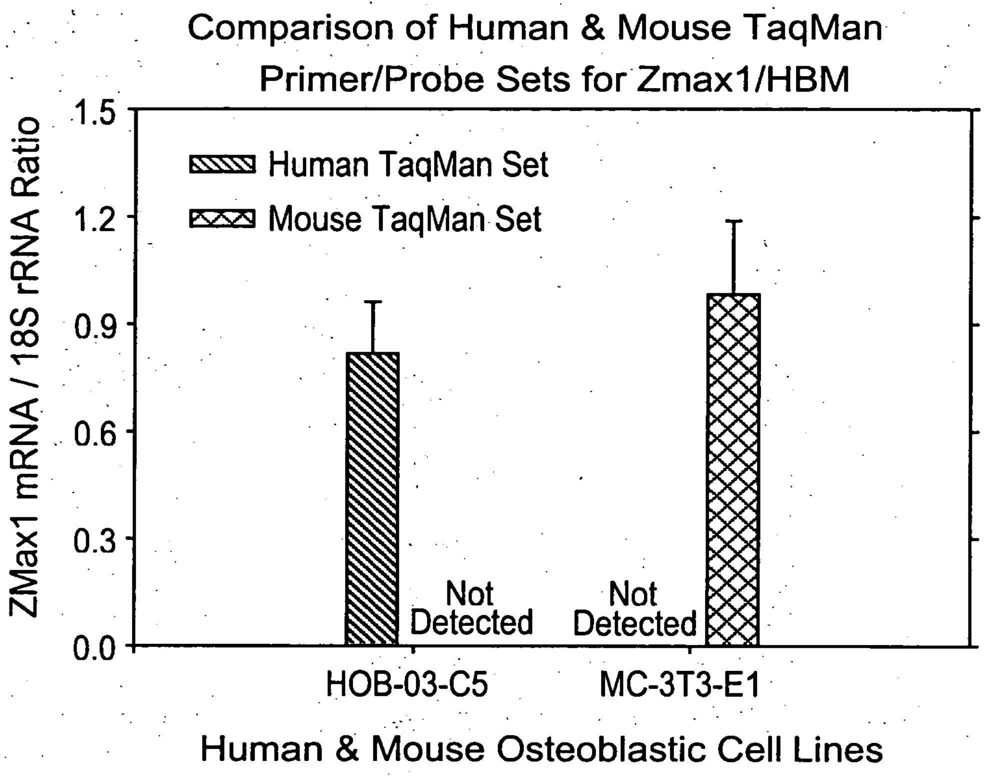

Comparison of Human & Mouse TaqMan Primer/Probe Sets for Zmax1/HBM
ZMax1 mRNA / 18S rRNA Ratio
1.5
1.2
0.9
0.6
0.3
0.0
▨ Human TaqMan Set
▩ Mouse TaqMan Set
Not Detected
Not Detected
HOB-03-C5
MC-3T3-E1
Human & Mouse Osteoblastic Cell Lines

FIG. 18

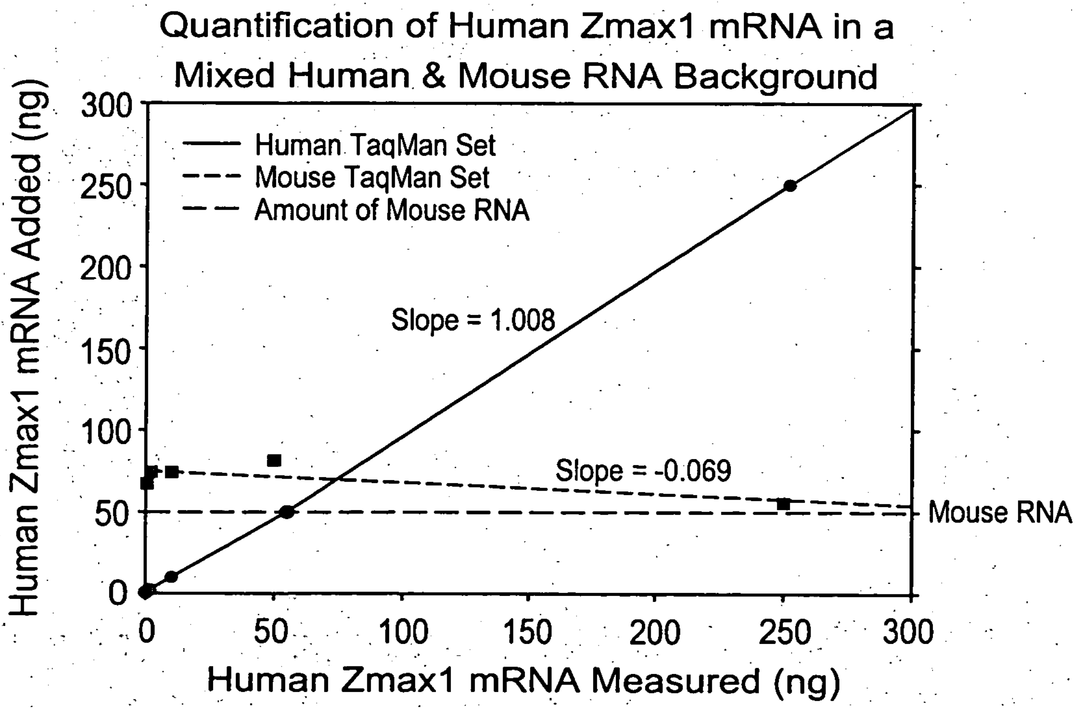

Quantification of Human Zmax1 mRNA in a Mixed Human & Mouse RNA Background
Human Zmax1 mRNA Added (ng)
300
250
200
150
100
50
0
Human TaqMan Set
Mouse TaqMan Set
Amount of Mouse RNA
Slope = 1.008
Slope = -0.069
Mouse RNA
0
50
100
150
200
250
300
Human Zmax1 mRNA Measured (ng)

FIG. 19

HBM: Transgenic mice

*mRNA expression by Taqman analysis**

	Tissue						
Line	Tibia	Femur	Heart	Gonad	Brain	Kidney	Liver
HBMMCBA							
2	7-10		20-90	2-30	6-11	5-9	<1
13	1-2		6-7	3-4	5-6	<1	<1
18	10-11						
HBMMTIC							
19	7-8	19-20	1				1
35	1	1	0				0

* relative to Zmax1 in HOB-03-C5

FIG. 20

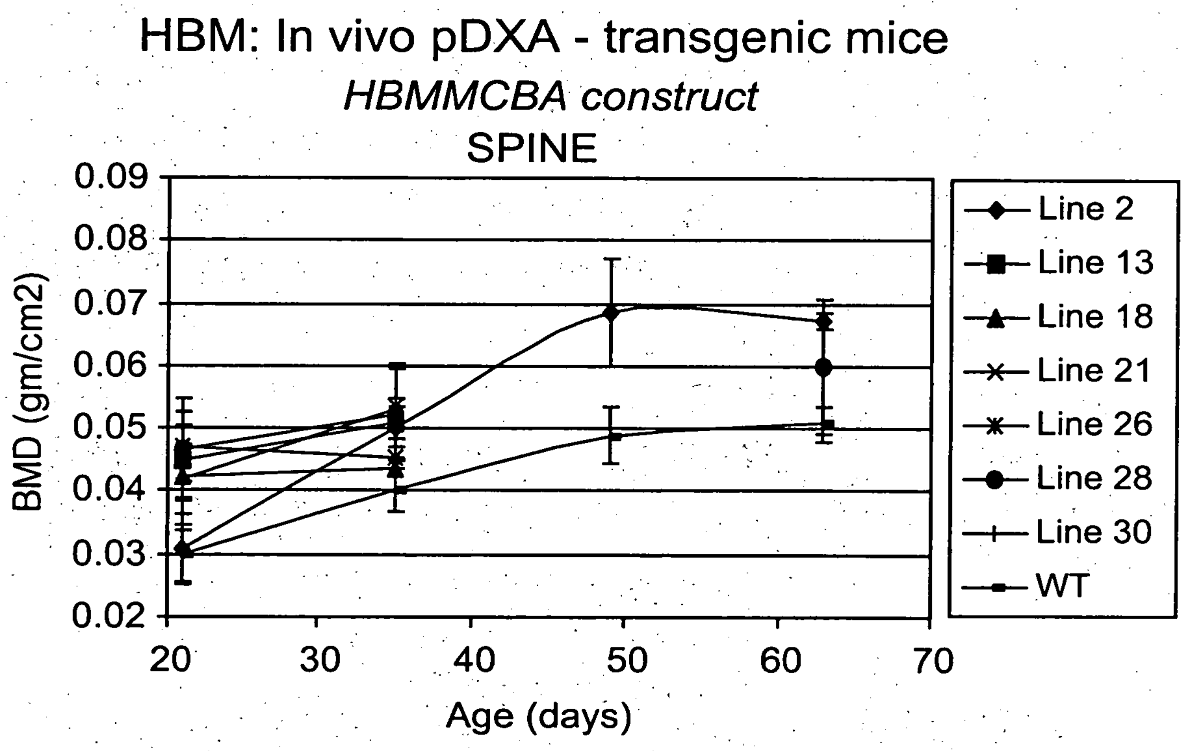


FIG. 21A

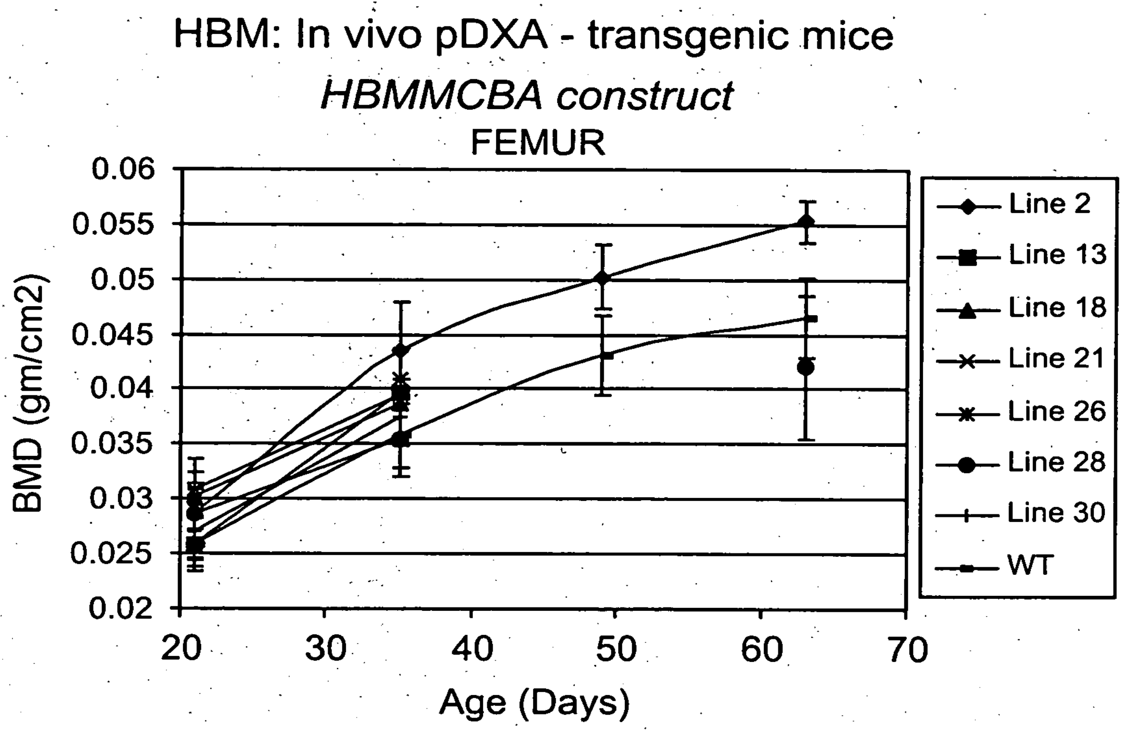


FIG. 21B

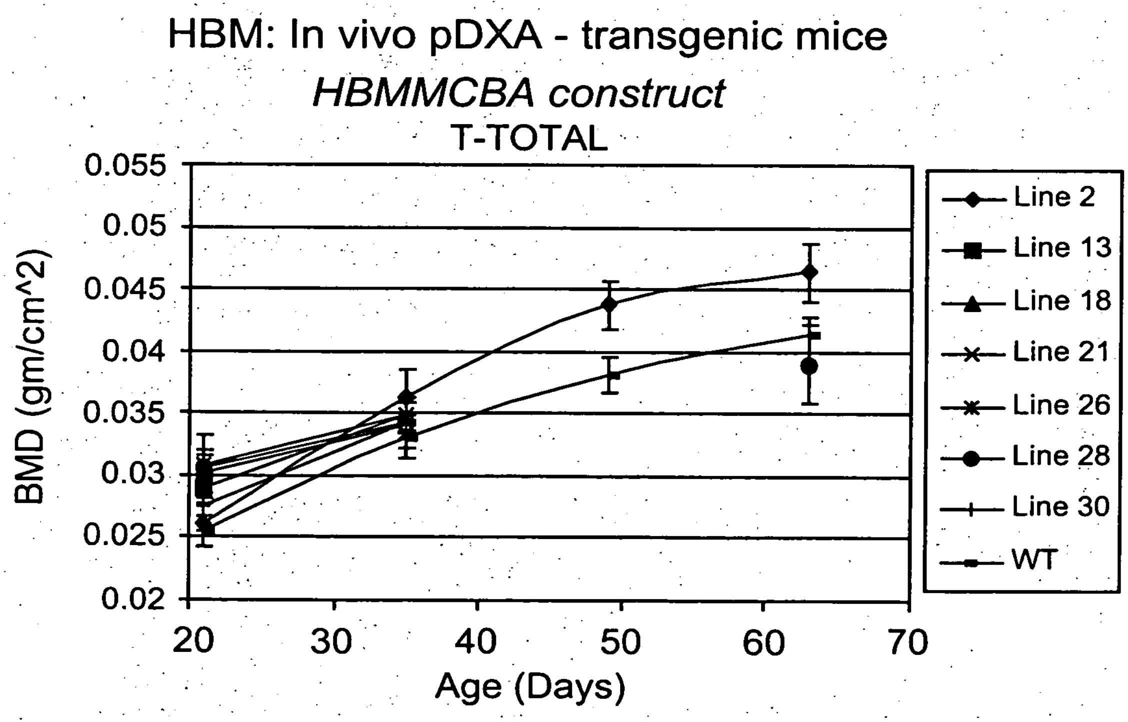


FIG. 21C

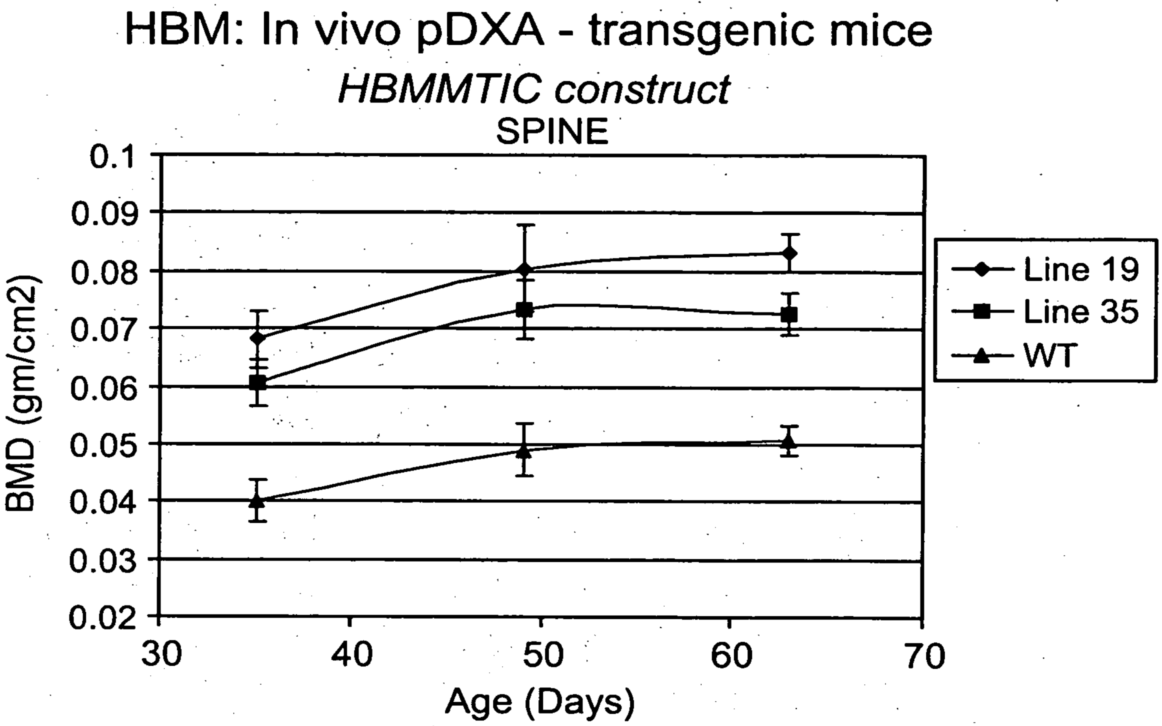


FIG. 21D

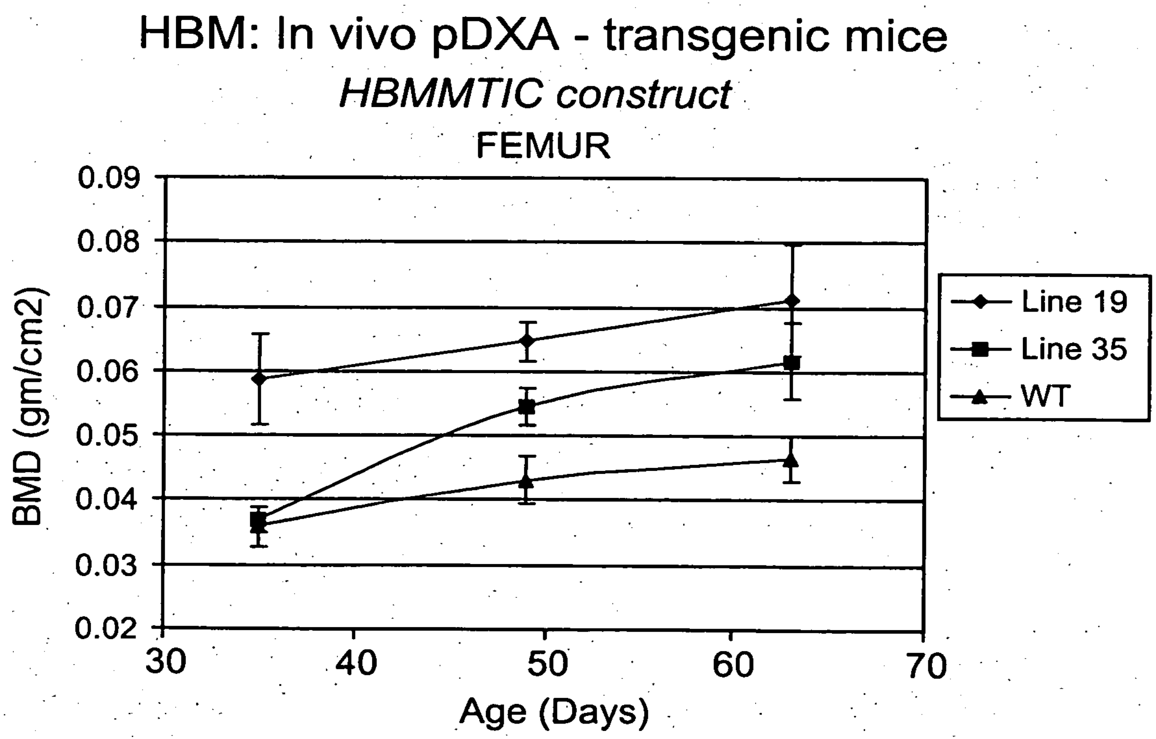


FIG. 21E

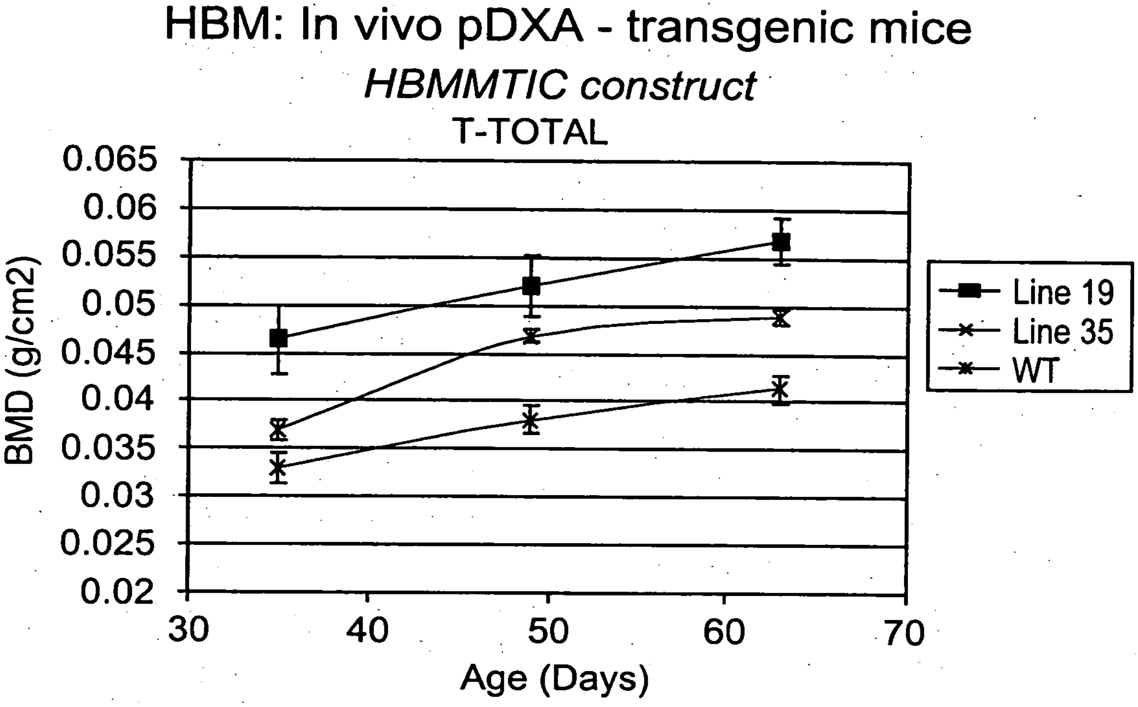

HBM: In vivo pDXA - transgenic mice
HBMMTIC construct
T-TOTAL
BMD (g/cm2)
0.065
0.06
0.055
0.05
0.045
0.04
0.035
0.03
0.025
0.02
30
40
50
60
70
Age (Days)
Line 19
Line 35
WT

FIG. 21F

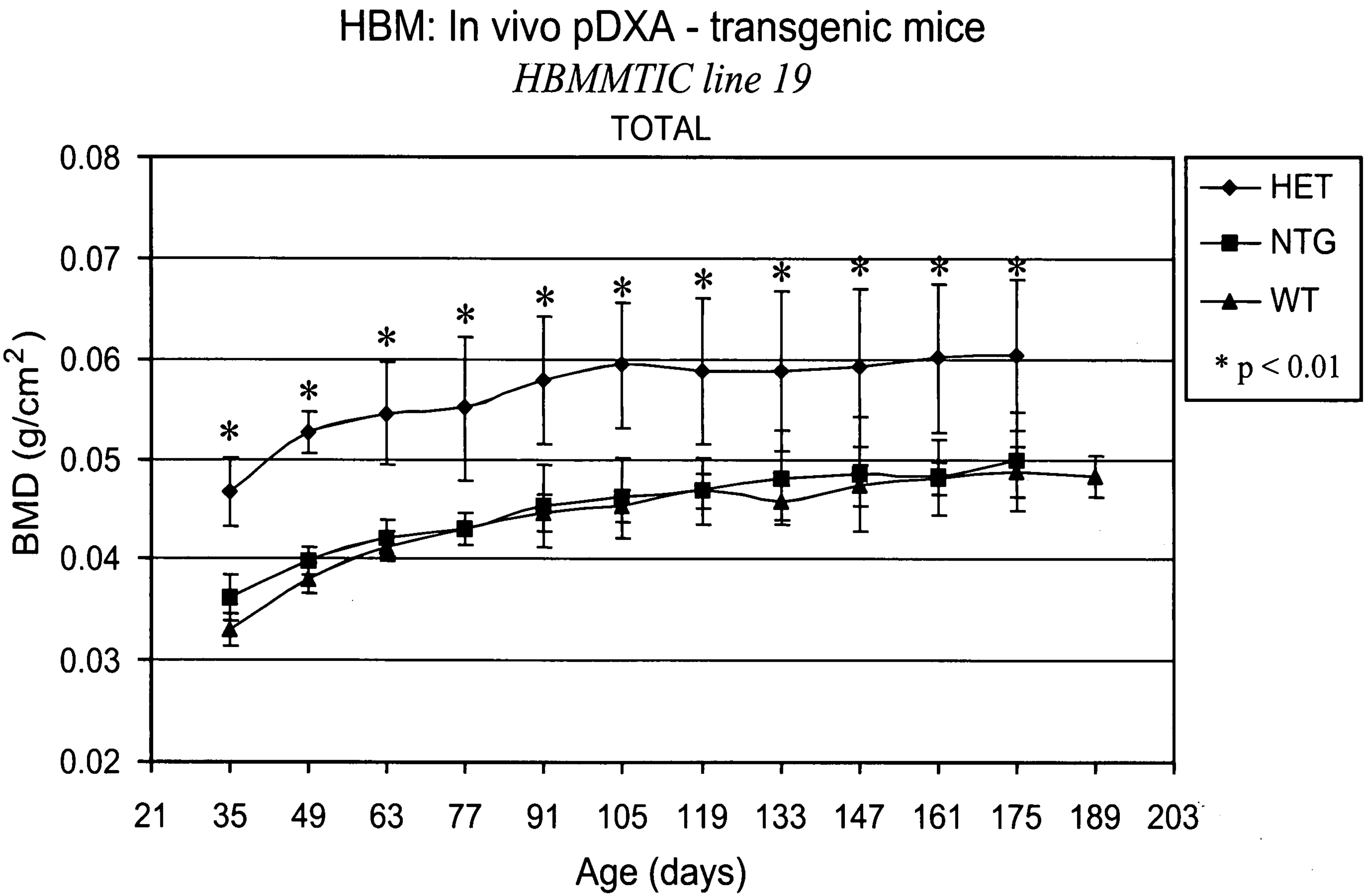

HBM: In vivo pDXA - transgenic mice
HBMMTIC line 19
TOTAL
BMD (g/cm²)
0.08
0.07
0.06
0.05
0.04
0.03
0.02
21
35
49
63
77
91
105
119
133
147
161
175
189
203
Age (days)
HET
NTG
WT
* p < 0.01
*

FIG. 21G

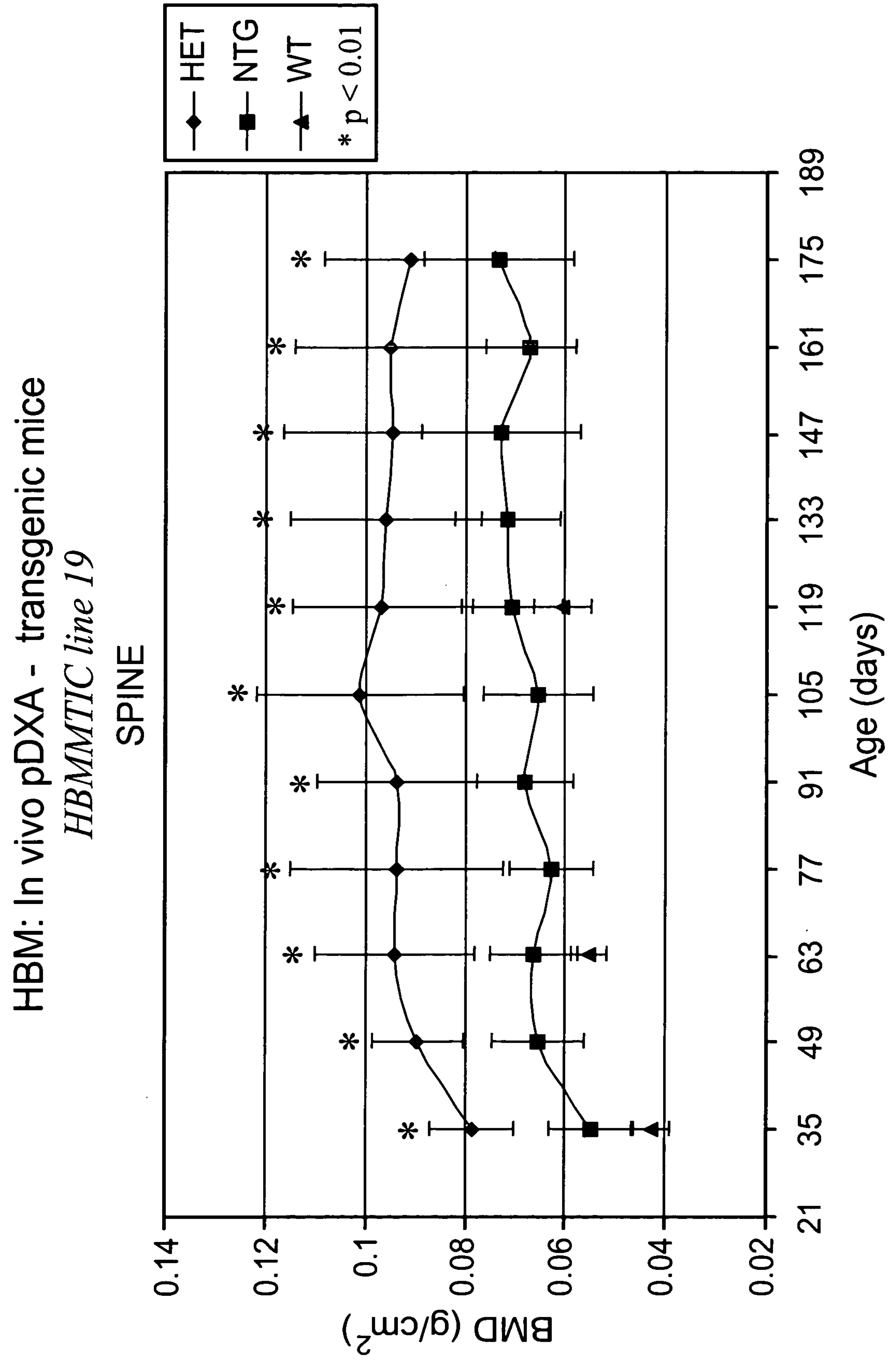

HBM: In vivo pDXA - transgenic mice
HBMMTIC line 19
SPINE
HET
NTG
WT
* p < 0.01
BMD (g/cm²)
0.14
0.12
0.1
0.08
0.06
0.04
0.02
21
35
49
63
77
91
105
119
133
147
161
175
189
Age (days)
*

FIG. 21H

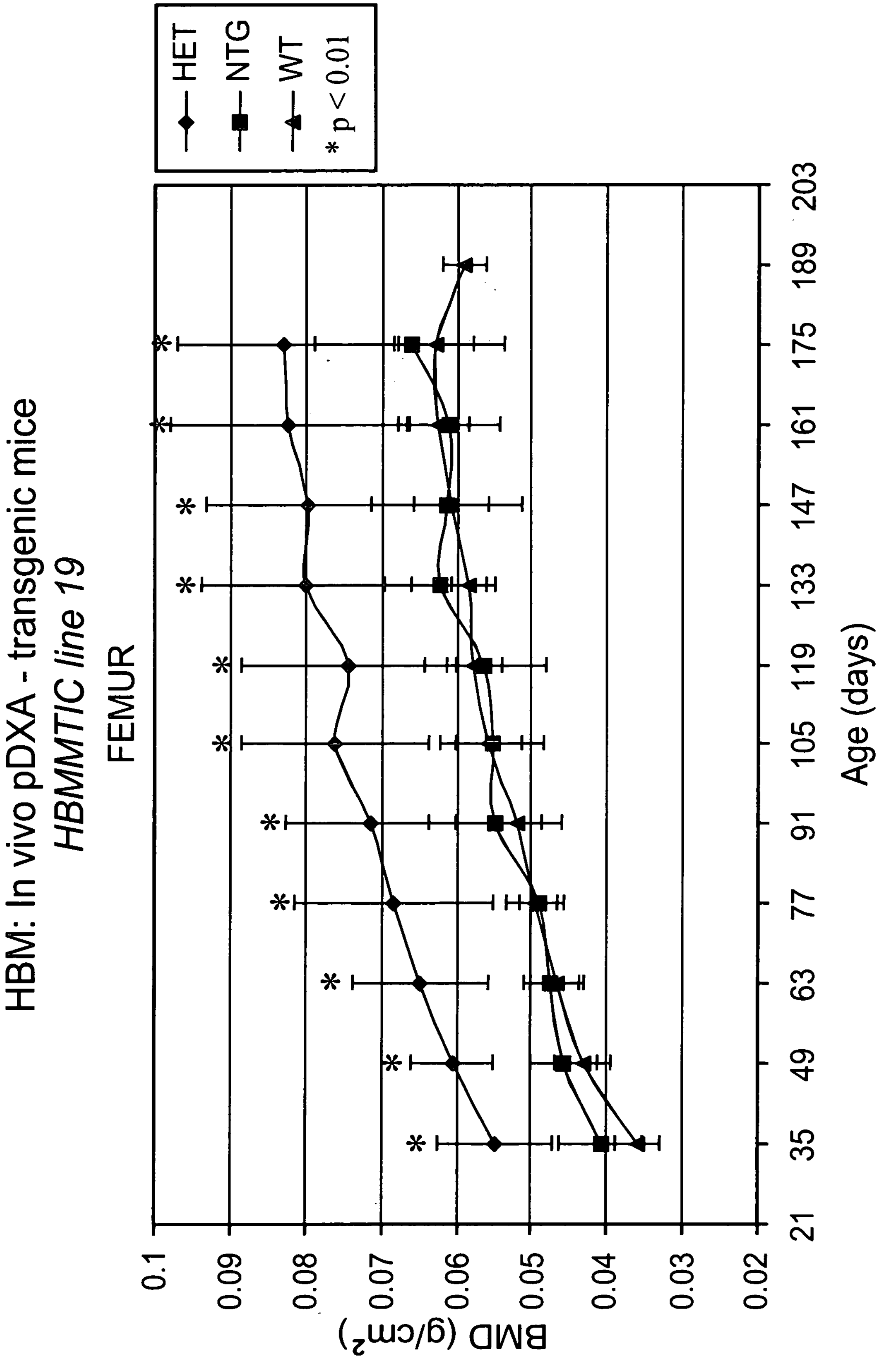

HBM: In vivo pDXA - transgenic mice
HBMMTIC line 19
FEMUR
HET
NTG
WT
* p < 0.01
BMD (g/cm²)
0.1
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
Age (days)
21
35
49
63
77
91
105
119
133
147
161
175
189
203
*

FIG. 21I

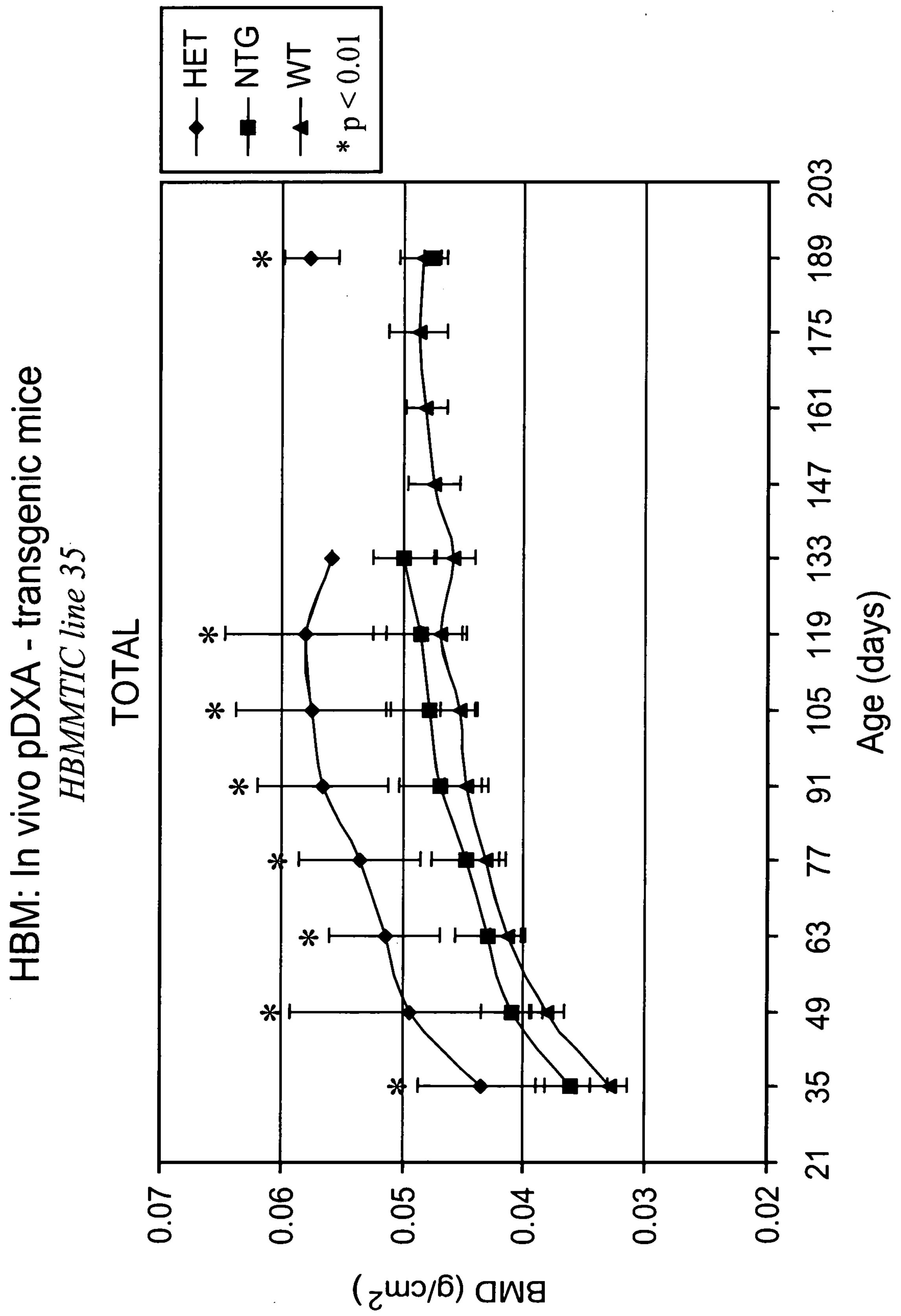

HBM: In vivo pDXA - transgenic mice
HBMMTIC line 35
TOTAL
HET
NTG
WT
* p < 0.01
BMD (g/cm²)
0.07
0.06
0.05
0.04
0.03
0.02
Age (days)
21
35
49
63
77
91
105
119
133
147
161
175
189
203
*

FIG. 21J

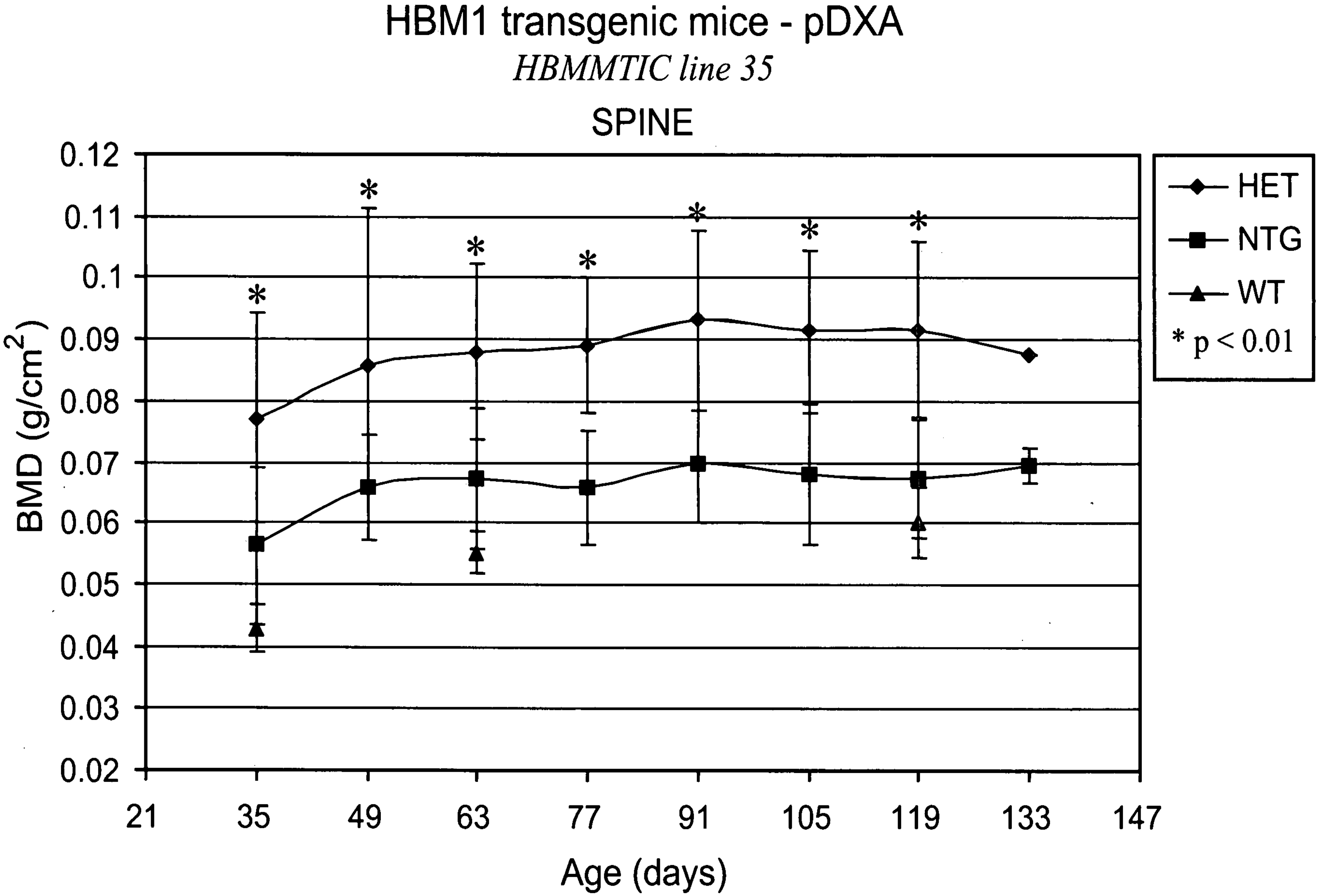

HBM1 transgenic mice - pDXA
HBMMTIC line 35
SPINE
BMD (g/cm^2)
0.12
0.11
0.1
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
21
35
49
63
77
91
105
119
133
147
Age (days)
HET
NTG
WT
* $p < 0.01$
*

FIG. 21K

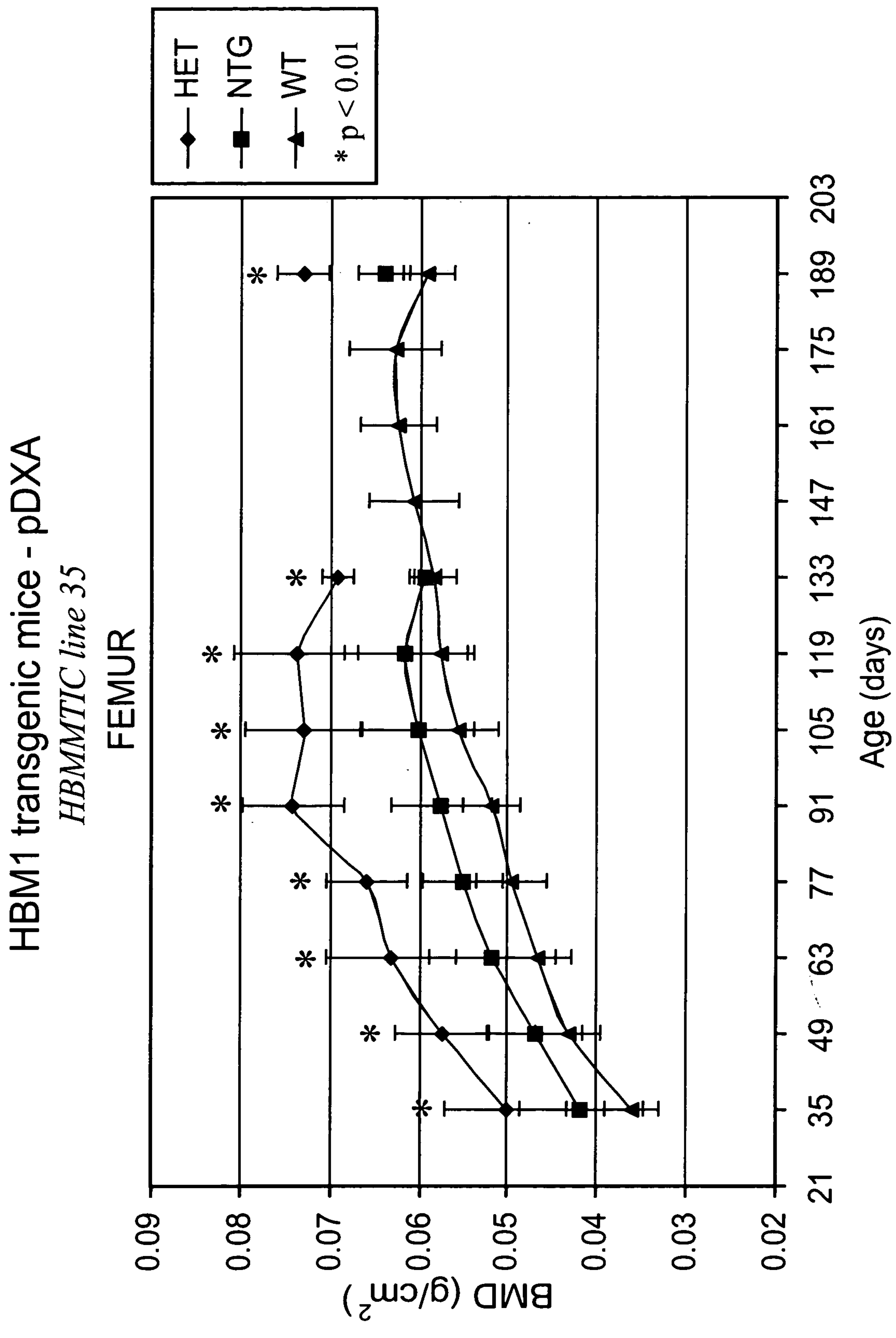

HBM1 transgenic mice - pDXA
HBMMTIC line 35
FEMUR
BMD (g/cm²)
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
Age (days)
21
35
49
63
77
91
105
119
133
147
161
175
189
203
HET
NTG
WT
* p < 0.01
*

FIG. 21L

HBM transgenic mice: in vivo pDXA*

BMD % changes vs WT in 5 week old animals

Line	n	Femur	Spine	Total	Tibia mRNA
HBMMCBA					
2	11	21	24	10	x7-10
13	4	11	27	5	x1-2
18	1	8	9	3	x10-11
21	1	10	12	6	0
28	15	0	30	4	x1
30	7	4	32	4	0
HBMMTIC					
19	5	63	70	41	x7-8
35	1	4	47	6	x1

** CV: Femur (2.7%); Spine (6.4%); Total (1.7%)*

FIG. 22

HBM transgenic mice: in vivo pDXA*

BMD % changes vs WT in 9 week old animals

Line	n	Femur	Spine	Total
HBMMCBA				
2	3	19	32	12
HBMMTIC				
19	2	52	64	37
35	3	32	43	18

** CV: Femur (2.7%); Spine (6.4%); Total (1.7%)*

FIG. 23

FIG. 24A

HBMGI_2AS

```
TCTAGACTCG AGGCGGCCGC CCATTGTGCA CTAAAGCGCC GCCGCCGCGC CATGGAGCCC
GAGTGAGCGC GGCGCGGGCC CGTCCGGCCG CCGGACAACA TGGAGGCAGC GCCGCCCGGG
CCGCCGTGGC CGCTGCTGCT GCTGCTGCTG CTGCTGCTGG CGCTGTGCGG CTGCCCGGCC
CCCGCCGCGG CCTCGCCGCT CCTGCTATTT GCCAACCGCC GGGACGTACG GCTGGTGGAC
GCCGGCGGAG TCAAGCTGGA GTCCACCATC GTGGTCAGCG GCCTGGAGGA TGCGGCCGCA
GTGGACTTCC AGTTTTCCAA GGGAGCCGTG TACTGGACAG ACGTGAGCGA GGAGGCCATC
AAGCAGACCT ACCTGAACCA GACGGGGGCC GCCGTGCAGA ACGTGGTCAT CTCCGGCCTG
GTCTCTCCCG ACGGCCTCGC CTGCGACTGG GTGGGCAAGA AGCTGTACTG GACGGACTCA
GAGACCAACC GCATCGAGGT GGCCAACCTC AATGGCACAT CCCGGAAGGT GCTCTTCTGG
CAGGACCTTG ACCAGCCGAG GGCCATCGCC TTGGACCCCG CTCACGGGTA CATGTACTGG
ACAGACTGGG TTGAGACGCC CCGGATTGAG CGGGCAGGGA TGGATGGCAG CACCCGGAAG
ATCATTGTGG ACTCGGACAT TTACTGGCCC AATGGACTGA CCATCGACCT GGAGGAGCAG
AAGCTCTACT GGGCTGACGC CAAGCTCAGC TTCATCCACC GTGCCAACCT GGACGGCTCG
TTCCGGCAGA AGGTGGTGGA GGGCAGCCTG ACGCACCCCT TCGCCCTGAC GCTCTCCGGG
GACACTCTGT ACTGGACAGA CTGGCAGACC CGCTCCATCC ATGCCTGCAA CAAGCGCACT
GGGGGGAAGA GGAAGGAGAT CCTGAGTGCC CTCTACTCAC CCATGGACAT CCAGGTGCTG
AGCCAGGAGC GGCAGCCTTT CTTCCACACT CGCTGTGAGG AGGACAATGG CGGCTGCTCC
CACCTGTGCC TGCTGTCCCC AAGCGAGCCT TTCTACACAT GCGCCTGCCC CACGGGTGTG
CAGCTGCAGG ACAACGGCAG GACGTGTAAG GCAGGAGCCG AGGAGGTGCT GCTGCTGGCC
CGGCGGACGG ACCTACGGAG GATCTCGCTG GACACGCCGG ACTTCACCGA CATCGTGCTG
CAGGTGGACG ACATCCGGCA CGCCATTGCC ATCGACTACG ACCCGCTAGA GGGCTATGTC
TACTGGACAG ATGACGAGGT GCGGGCCATC CGCAGGGCGT ACCTGGACGG GTCTGGGGCG
CAGACGCTGG TCAACACCGA GATCAACGAC CCCGATGGCA TCGCGGTCGA CTGGGTGGCC
CGAAACCTCT ACTGGACCGA CACGGGCACG GACCGCATCG AGGTGACGCG CCTCAACGGC
```

FIG. 24B

HBMGI_2AS

```
ACCTCCCGCA AGATCCTGGT GTCGGAGGAC CTGGACGAGC CCCGAGCCAT CGCACTGCAC
CCCGTGATGG GCCTCATGTA CTGGACAGAC TGGGGAGAGA ACCCTAAAAT CGAGTGTGCC
AACTTGGATG GGCAGGAGCG GCGTGTGCTG GTCAATGCCT CCCTCGGGTG GCCCAACGGC
CTGGCCCTGG ACCTGCAGGA GGGGAAGCTC TACTGGGGAG ACGCCAAGAC AGACAAGATC
GAGGTGATCA ATGTTGATGG GACGAAGAGG CGGACCCTCC TGGAGGACAA GCTCCCGCAC
ATTTTCGGGT TCACGCTGCT GGGGGACTTC ATCTACTGGA CTGACTGGCA GCGCCGCAGC
ATCGAGCGGG TGCACAAGGT CAAGGCCAGC CGGGACGTCA TCATTGACCA GCTGCCCGAC
CTGATGGGGC TCAAAGCTGT GAATGTGGCC AAGGTCGTCG GAACCAACCC GTGTGCGGAC
AGGAACGGGG GGTGCAGCCA CCTGTGCTTC TTCACACCCC ACGCAACCCG GTGTGGCTGC
CCCATCGGCC TGGAGCTGCT GAGTGACATG AAGACCTGCA TCGTGCCTGA GGCCTTCTTG
GTCTTCACCA GCAGAGCCGC CATCCACAGG ATCTCCCTCG AGACCAATAA CAACGACGTG
GCCATCCCGC TCACGGGCGT CAAGGAGGCC TCAGCCCTGG ACTTTGATGT GTCCAACAAC
CACATCTACT GGACAGACGT CAGCCTGAAG ACCATCAGCC GCGCCTTCAT GAACGGGAGC
TCGGTGGAGC ACGTGGTGGA GTTTGGCCTT GACTACCCCG AGGGCATGGC CGTTGACTGG
ATGGGCAAGA ACCTCTACTG GGCCGACACT GGGACCAACA GAATCGAAGT GGCGCGGCTG
GACGGGCAGT TCCGGCAAGT CCTCGTGTGG AGGGACTTGG ACAACCCGAG GTCGCTGGCC
CTGGATCCCA CCAAGGGCTA CATCTACTGG ACCGAGTGGG GCGGCAAGCC GAGGATCGTG
CGGGCCTTCA TGGACGGGAC CAACTGCATG ACGCTGGTGG ACAAGGTGGG CCGGGCCAAC
GACCTCACCA TTGACTACGC TGACCAGCGC CTCTACTGGA CCGACCTGGA CACCAACATG
ATCGAGTCGT CCAACATGCT GGGTCAGGAG CGGGTCGTGA TTGCCGACGA TCTCCCGCAC
CCGTTCGGTC TGACGCAGTA CAGCGATTAT ATCTACTGGA CAGACTGGAA TCTGCACAGC
ATTGAGCGGG CCGACAAGAC TAGCGGCCGG AACCGCACCC TCATCCAGGG CCACCTGGAC
TTCGTGATGG ACATCCTGGT GTTCCACTCC TCCCGCCAGG ATGGCCTCAA TGACTGTATG
```

FIG. 24C

HBMGI_2AS

```
CACAACAACG GGCAGTGTGG GCAGCTGTGC CTTGCCATCC CCGGCGGCCA CCGCTGCGGC
TGGGCCTCAC ACTACACCCT GGACCCCAGC AGCCGCAACT GCAGCCCGCC CACCACCTTC
TTGCTGTTCA GCCAGAAATC TGCCATCAGT CGGATGATCC CGGACGACCA GCACAGCCCG
GATCTCATCC TGCCCCTGCA TGGACTGAGG AACGTCAAAG CCATCGACTA TGACCCACTG
GACAAGTTCA TCTACTGGGT GGATGGGCGC CAGAACATCA AGCGAGCCAA GGACGACGGG
ACCCAGCCCT TTGTTTTGAC CTCTCTGAGC CAAGGCCAAA ACCCAGACAG GCAGCCCCAC
GACCTCAGCA TCGACATCTA CAGCCGGACA CTGTTCTGGA CGTGCGAGGC CACCAATACC
ATCAACGTCC ACAGGCTGAG CGGGGAAGCC ATGGGGGTGG TGCTGCGTGG GGACCGCGAC
AAGCCCAGGG CCATCGTCGT CAACGCGGAG CGAGGGTACC TGTACTTCAC CAACATGCAG
GACCGGGCAG CCAAGATCGA ACGCGCAGCC CTGGACGGCA CCGAGCGCGA GGTCCTCTTC
ACCACCGGCC TCATCCGCCC TGTGGCCCTG GTGGTAGACA ACACACTGGG CAAGCTGTTC
TGGGTGGACG CGGACCTGAA GCGCATTGAG AGCTGTGACC TGTCAGGGGC CAACCGCCTG
ACCCTGGAGG ACGCCAACAT CGTGCAGCCT CTGGGCCTGA CCATCCTTGG CAAGCATCTC
TACTGGATCG ACCGCCAGCA GCAGATGATC GAGCGTGTGG AGAAGACCAC CGGGGACAAG
CGGACTCGCA TCCAGGGCCG TGTCGCCCAC CTCACTGGCA TCCATGCAGT GGAGGAAGTC
AGCCTGGAGG AGTTCTCAGC CCACCCATGT GCCCGTGACA ATGGTGGCTG CTCCCACATC
TGTATTGCCA AGGGTGATGG GACACCACGG TGCTCATGCC CAGTCCACCT CGTGCTCCTG
CAGAACCTGC TGACCTGTGG AGAGCCGCCC ACCTGCTCCC CGGACCAGTT TGCATGTGCC
ACAGGGGAGA TCGACTGTAT CCCCGGGGCC TGGCGCTGTG ACGGCTTTCC CGAGTGCGAT
GACCAGAGCG ACGAGGAGGG CTGCCCCGTG TGCTCCGCCG CCCAGTTCCC CTGCGCGCGG
GGTCAGTGTG TGGACCTGCG CCTGCGCTGC GACGGCGAGG CAGACTGTCA GGACCGCTCA
GACGAGGCGG ACTGTGACGC CATCTGCCTG CCCAACCAGT TCCGGTGTGC GAGCGGCCAG
TGTGTCCTCA TCAAACAGCA GTGCGACTCC TTCCCCGACT GTATCGACGG CTCCGACGAG
CTCATGTGTG AAATCACCAA GCCGCCCTCA GACGACAGCC CGGCCCACAG CAGTGCCATC
```

FIG. 24D

HBMGI_2AS

```
GGGCCCGTCA TTGGCATCAT CCTCTCTCTC TTCGTCATGG GTGGTGTCTA TTTTGTGTGC
CAGCGCGTGG TGTGCCAGCG CTATGCGGGG GCCAACGGGC CCTTCCCGCA CGAGTATGTC
AGCGGGACCC CGCACGTGCC CCTCAATTTC ATAGCCCCGG GCGGTTCCCA GCATGGCCCC
TTCACAGGCA TCGCATGCGG AAAGTCCATG ATGAGCTCCG TGAGCCTGAT GGGGGGCCGG
GGCGGGGTGC CCCTCTACGA CCGGAACCAC GTCACAGGGG CCTCGTCCAG CAGCTCGTCC
AGCACGAAGG CCACGCTGTA CCCGCCGATC CTGAACCCGC CGCCCTCCCC GGCCACGGAC
CCCTCCCTGT ACAACATGGA CATGTTCTAC TCTTCAAACA TTCCGGCCAC TGCGAGACCG
TACAGGCCCT ACATCATTCG AGGAATGGCG CCCCCGACGA CGCCCTGCAG CACCGACGTG
TGTGACAGCG ACTACAGCGC CAGCCGCTGG AAGGCCAGCA AGTACTACCT GGATTTGAAC
TCGGACTCAG ACCCCTATCC ACCCCCACCC ACGCCCCACA GCCAGTACCT GTCGGCGGAG
GACAGCTGCC CGCCCTCGCC CGCCACCGAG AGGAGCTACT TCCATCTCTT CCCGCCCCCT
CCGTCCCCCT GCACGGACTC ATCCTGACCT CGGCCGGGCC ACTCTGGCTT CTCTGTGCCC
CTGTAAATAG TTTTAAATAT GAACAAAGAA AAAAATATAT TTTATGATTT AAAAAATAAA
TATAATTGGG ATTTTAAAAA CATGAGAAAT GTGAACTGTG ATGGGGTGGG CAGGGCTGGG
AGAACTTTGT ACAGTGGAGA AATATTTATA AACTTAATTT TGTAAAACAG AAAAAAAAAA
AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA
AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA GCGGCCGC
```

FIG. 25A

ZMAXGI_3AS

```
TCTAGACTCG AGGCGGCCGC CCATTGTGCA CTAAAGCGCC GCCGCCGCGC CATGGAGCCC
GAGTGAGCGC GGCGCGGGCC CGTCCGGCCG CCGGACAACA TGGAGGCAGC GCCGCCCGGG
CCGCCGTGGC CGCTGCTGCT GCTGCTGCTG CTGCTGCTGG CGCTGTGCGG CTGCCCGGCC
CCCGCCGCGG CCTCGCCGCT CCTGCTATTT GCCAACCGCC GGGACGTACG GCTGGTGGAC
GCCGGCGGAG TCAAGCTGGA GTCCACCATC GTGGTCAGCG GCCTGGAGGA TGCGGCCGCA
GTGGACTTCC AGTTTTCCAA GGGAGCCGTG TACTGGACAG ACGTGAGCGA GGAGGCCATC
AAGCAGACCT ACCTGAACCA GACGGGGGCC GCCGTGCAGA ACGTGGTCAT CTCCGGCCTG
GTCTCTCCCG ACGGCCTCGC CTGCGACTGG GTGGGCAAGA AGCTGTACTG GACGGACTCA
GAGACCAACC GCATCGAGGT GGCCAACCTC AATGGCACAT CCCGGAAGGT GCTCTTCTGG
CAGGACCTTG ACCAGCCGAG GGCCATCGCC TTGGACCCCG CTCACGGGTA CATGTACTGG
ACAGACTGGG GTGAGACGCC CCGGATTGAG CGGGCAGGGA TGGATGGCAG CACCCGGAAG
ATCATTGTGG ACTCGGACAT TTACTGGCCC AATGGACTGA CCATCGACCT GGAGGAGCAG
AAGCTCTACT GGGCTGACGC CAAGCTCAGC TTCATCCACC GTGCCAACCT GGACGGCTCG
TTCCGGCAGA AGGTGGTGGA GGGCAGCCTG ACGCACCCCT TCGCCCTGAC GCTCTCCGGG
GACACTCTGT ACTGGACAGA CTGGCAGACC CGCTCCATCC ATGCCTGCAA CAAGCGCACT
GGGGGGAAGA GGAAGGAGAT CCTGAGTGCC CTCTACTCAC CCATGGACAT CCAGGTGCTG
AGCCAGGAGC GGCAGCCTTT CTTCCACACT CGCTGTGAGG AGGACAATGG CGGCTGCTCC
CACCTGTGCC TGCTGTCCCC AAGCGAGCCT TTCTACACAT GCGCCTGCCC CACGGGTGTG
CAGCTGCAGG ACAACGGCAG GACGTGTAAG GCAGGAGCCG AGGAGGTGCT GCTGCTGGCC
CGGCGGACGG ACCTACGGAG GATCTCGCTG GACACGCCGG ACTTCACCGA CATCGTGCTG
CAGGTGGACG ACATCCGGCA CGCCATTGCC ATCGACTACG ACCCGCTAGA GGGCTATGTC
TACTGGACAG ATGACGAGGT GCGGGCCATC CGCAGGGCGT ACCTGGACGG GTCTGGGGCG
CAGACGCTGG TCAACACCGA GATCAACGAC CCCGATGGCA TCGCGGTCGA CTGGGTGGCC
CGAAACCTCT ACTGGACCGA CACGGGCACG GACCGCATCG AGGTGACGCG CCTCAACGGC
```

FIG. 25B

ZMAXGI_3AS

```
ACCTCCCGCA AGATCCTGGT GTCGGAGGAC CTGGACGAGC CCCGAGCCAT CGCACTGCAC
CCCGTGATGG GCCTCATGTA CTGGACAGAC TGGGGAGAGA ACCCTAAAAT CGAGTGTGCC
AACTTGGATG GGCAGGAGCG GCGTGTGCTG GTCAATGCCT CCCTCGGGTG GCCCAACGGC
CTGGCCCTGG ACCTGCAGGA GGGGAAGCTC TACTGGGGAG ACGCCAAGAC AGACAAGATC
GAGGTGATCA ATGTTGATGG GACGAAGAGG CGGACCCTCC TGGAGGACAA GCTCCCGCAC
ATTTTCGGGT TCACGCTGCT GGGGGACTTC ATCTACTGGA CTGACTGGCA GCGCCGCAGC
ATCGAGCGGG TGCACAAGGT CAAGGCCAGC CGGGACGTCA TCATTGACCA GCTGCCCGAC
CTGATGGGGC TCAAAGCTGT GAATGTGGCC AAGGTCGTCG GAACCAACCC GTGTGCGGAC
AGGAACGGGG GGTGCAGCCA CCTGTGCTTC TTCACACCCC ACGCAACCCG GTGTGGCTGC
CCCATCGGCC TGGAGCTGCT GAGTGACATG AAGACCTGCA TCGTGCCTGA GGCCTTCTTG
GTCTTCACCA GCAGAGCCGC CATCCACAGG ATCTCCCTCG AGACCAATAA CAACGACGTG
GCCATCCCGC TCACGGGCGT CAAGGAGGCC TCAGCCCTGG ACTTTGATGT GTCCAACAAC
CACATCTACT GGACAGACGT CAGCCTGAAG ACCATCAGCC GCGCCTTCAT GAACGGGAGC
TCGGTGGAGC ACGTGGTGGA GTTTGGCCTT GACTACCCCG AGGGCATGGC CGTTGACTGG
ATGGGCAAGA ACCTCTACTG GGCCGACACT GGGACCAACA GAATCGAAGT GGCGCGGCTG
GACGGGCAGT TCCGGCAAGT CCTCGTGTGG AGGGACTTGG ACAACCCGAG GTCGCTGGCC
CTGGATCCCA CCAAGGGCTA CATCTACTGG ACCGAGTGGG GCGGCAAGCC GAGGATCGTG
CGGGCCTTCA TGGACGGGAC CAACTGCATG ACGCTGGTGG ACAAGGTGGG CCGGGCCAAC
GACCTCACCA TTGACTACGC TGACCAGCGC CTCTACTGGA CCGACCTGGA CACCAACATG
ATCGAGTCGT CCAACATGCT GGGTCAGGAG CGGGTCGTGA TTGCCGACGA TCTCCCGCAC
CCGTTCGGTC TGACGCAGTA CAGCGATTAT ATCTACTGGA CAGACTGGAA TCTGCACAGC
ATTGAGCGGG CCGACAAGAC TAGCGGCCGG AACCGCACCC TCATCCAGGG CCACCTGGAC
TTCGTGATGG ACATCCTGGT GTTCCACTCC TCCCGCCAGG ATGGCCTCAA TGACTGTATG
```

FIG. 25C

ZMAXGI_3AS

```
CACAACAACG GGCAGTGTGG GCAGCTGTGC CTTGCCATCC CCGGCGGCCA CCGCTGCGGC
TGCGCCTCAC ACTACACCCT GGACCCCAGC AGCCGCAACT GCAGCCCGCC CACCACCTTC
TTGCTGTTCA GCCAGAAATC TGCCATCAGT CGGATGATCC CGGACGACCA GCACAGCCCG
GATCTCATCC TGCCCCTGCA TGGACTGAGG AACGTCAAAG CCATCGACTA TGACCCACTG
GACAAGTTCA TCTACTGGGT GGATGGGCGC CAGAACATCA AGCGAGCCAA GGACGACGGG
ACCCAGCCCT TTGTTTTGAC CTCTCTGAGC CAAGGCCAAA ACCCAGACAG GCAGCCCCAC
GACCTCAGCA TCGACATCTA CAGCCGGACA CTGTTCTGGA CGTGCGAGGC CACCAATACC
ATCAACGTCC ACAGGCTGAG CGGGGAAGCC ATGGGGGTGG TGCTGCGTGG GGACCGCGAC
AAGCCCAGGG CCATCGTCGT CAACGCGGAG CGAGGGTACC TGTACTTCAC CAACATGCAG
GACCGGGCAG CCAAGATCGA ACGCGCAGCC CTGGACGGCA CCGAGCGCGA GGTCCTCTTC
ACCACCGGCC TCATCCGCCC TGTGGCCCTG GTGGTAGACA ACACACTGGG CAAGCTGTTC
TGGGTGGACG CGGACCTGAA GCGCATTGAG AGCTGTGACC TGTCAGGGGC CAACCGCCTG
ACCCTGGAGG ACGCCAACAT CGTGCAGCCT CTGGGCCTGA CCATCCTTGG CAAGCATCTC
TACTGGATCG ACCGCCAGCA GCAGATGATC GAGCGTGTGG AGAAGACCAC CGGGGACAAG
CGGACTCGCA TCCAGGGCCG TGTCGCCCAC CTCACTGGCA TCCATGCAGT GGAGGAAGTC
AGCCTGGAGG AGTTCTCAGC CCACCCATGT GCCCGTGACA ATGGTGGCTG CTCCCACATC
TGTATTGCCA AGGGTGATGG GACACCACGG TGCTCATGCC CAGTCCACCT CGTGCTCCTG
CAGAACCTGC TGACCTGTGG AGAGCCGCCC ACCTGCTCCC CGGACCAGTT TGCATGTGCC
ACAGGGGAGA TCGACTGTAT CCCCGGGGCC TGGCGCTGTG ACGGCTTTCC CGAGTGCGAT
GACCAGAGCG ACGAGGAGGG CTGCCCCGTG TGCTCCGCCGC CCAGTTCCCC TGCGCGCGG
GGTCAGTGTGT GGACCTGCGC CTGCGCTGCG ACGGCGAGGC AGACTGTCAG GACCGCTCA
GACGAGGCGGA CTGTGACGCC ATCTGCCTGC CCAACCAGTT CCGGTGTGCG AGCGGCCAG
TGTGTCCTCAT CAAACAGCAG TGCGACTCCT TCCCCGACTG TATCGACGGC TCCGACGAG
CTCATGTGTGA AATCACCAAG CCGCCCTCAG ACGACAGCCC GGCCCACAGC AGTGCCATC
```

FIG. 25D

ZMAXGI_3AS

```
GGGCCCGTCA TTGGCATCAT CCTCTCTCTC TTCGTCATGG GTGGTGTCTA TTTTGTGTGC
CAGCGCGTGG TGTGCCAGCG CTATGCGGGG GCCAACGGGC CCTTCCCGCA CGAGTATGTC
AGCGGGACCC CGCACGTGCC CCTCAATTTC ATAGCCCCGG GCGGTTCCCA GCATGGCCCC
TTCACAGGCA TCGCATGCGG AAAGTCCATG ATGAGCTCCG TGAGCCTGAT GGGGGGCCGG
GGCGGGGTGC CCCTCTACGA CCGGAACCAC GTCACAGGGG CCTCGTCCAG CAGCTCGTCC
AGCACGAAGG CCACGCTGTA CCCGCCGATC CTGAACCCGC CGCCCTCCCC GGCCACGGAC
CCCTCCCTGT ACAACATGGA CATGTTCTAC TCTTCAAACA TTCCGGCCAC TGCGAGACCG
TACAGGCCCT ACATCATTCG AGGAATGGCG CCCCCGACGA CGCCCTGCAG CACCGACGTG
TGTGACAGCG ACTACAGCGC CAGCCGCTGG AAGGCCAGCA AGTACTACCT GGATTTGAAC
TCGGACTCAG ACCCCTATCC ACCCCCACCC ACGCCCCACA GCCAGTACCT GTCGGCGGAG
GACAGCTGCC CGCCCTCGCC CGCCACCGAG AGGAGCTACT TCCATCTCTT CCCGCCCCCT
CCGTCCCCCT GCACGGACTC ATCCTGACCT CGGCCGGGCC ACTCTGGCTT CTCTGTGCCC
CTGTAAATAG TTTTAAATAT GAACAAAGAA AAAAATATAT TTTATGATTT AAAAAATAAA
TATAATTGGG ATTTTAAAAA CATGAGAAAT GTGAACTGTG ATGGGGTGGG CAGGGCTGGG
AGAACTTTGT ACAGTGGAGA AATATTTATA AACTTAATTT TGTAAAACAG AAAAAAAAAA
AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA
AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA GCGGCCGC
```

FIG. 26A

Alignment of Human and Mouse Zmax1 (LRP5)
Amino-Acid Sequences.
Top= Human, Bottom = Mouse

```
              .         .         .         .         .
   1 MEA....APPGPPWPLLLLLLLLLALCGCPAPAAASPLLLFANRRDVRLV 46
     ||.    |||.|| |||||:     |:.: .||||||||||||||||||
   1 METAPTRAPPPPPPPLLLLV.....LYCSLVPAAASPLLLFANRRDVRLV 45

              .         .         .         .         .
  47 DAGGVKLESTIVVSGLEDAAAVDFQFSKGAVYWTDVSEEAIKQTYLNQTG 96
     ||||||||||||.|||||||||||||||||||||||||||||||||||||
  46 DAGGVKLESTIVASGLEDAAAVDFQFSKGAVYWTDVSEEAIKQTYLNQTG 95

              .         .         .         .         .
  97 AAVQNVVISGLVSPDGLACDWVGKKLYWTDSETNRIEVANLNGTSRKVLF 146
     ||.||:||||||||||||||||||||||||||||||||||||||||||||
  96 AAAQNIVISGLVSPDGLACDWVGKKLYWTDSETNRIEVANLNGTSRKVLF 145

              .         .         .         .         .
 147 WQDLDQPRAIALDPAHGYMYWTDWGETPRIERAGMDGSTRKIIVDSDIYW 196
     ||||||||||||||||||||||||||.|||||||||||||||||||||||
 146 WQDLDQPRAIALDPAHGYMYWTDWGEAPRIERAGMDGSTRKIIVDSDIYW 195

              .         .         .         .         .
 197 PNGLTIDLEEQKLYWADAKLSFIHRANLDGSFRQKVVEGSLTHPFALTLS 246
     ||||||||||||||||||||||||||||||||||||||||||||||||||
 196 PNGLTIDLEEQKLYWADAKLSFIHRANLDGSFRQKVVEGSLTHPFALTLS 245

              .         .         .         .         .
 247 GDTLYWTDWQTRSIHACNKRTGGKRKEILSALYSPMDIQVLSQERQPFFH 296
     |||||||||||||||||||:||:.||||||||||||||||||||||| ||
 246 GDTLYWTDWQTRSIHACNKWTGEQRKEILSALYSPMDIQVLSQERQPPFH 295

              .         .         .         .         .
 297 TRCEEDNGGCSHLCLLSPSEPFYTCACPTGVQLQDNGRTCKAGAEEVLLL 346
     |.||||||||||||||||.||||.|||||||||||||:|||.||||||||
 296 TPCEEDNGGCSHLCLLSPREPFYSCACPTGVQLQDNGKTCKTGAEEVLLL 345

              .         .         .         .         .
 347 ARRTDLRRISLDTPDFTDIVLQVDDIRHAIAIDYDPLEGYVYWTDDEVRA 396
     |||||||||||||||||||||||:||||||||||||||||||||||||||
 346 ARRTDLRRISLDTPDFTDIVLQVGDIRHAIAIDYDPLEGYVYWTDDEVRA 395

              .         .         .         .         .
 397 IRRAYLDGSGAQTLVNTEINDPDGIAVDWVARNLYWTDTGTDRIEVTRLN 446
     ||||||||||||||||||||||||||||||||||||||||||||||||||
 396 IRRAYLDGSGAQTLVNTEINDPDGIAVDWVARNLYWTDTGTDRIEVTRLN 445

              .         .         .         .         .
 447 GTSRKILVSEDLDEPRAIALHPVMGLMYWTDWGENPKIECANLDGQERRV 496
     ||||||||||||||||||.||||||||||||||||||||||||||.:|:|
 446 GTSRKILVSEDLDEPRAIVLHPVMGLMYWTDWGENPKIECANLDGRDRHV 495

              .         .         .         .         .
 497 LVNASLGWPNGLALDLQEGKLYWGDAKTDKIEVINVDGTKRRTLLEDKLP 546
     |||.|||||||||||||||||||||||||||||||:|||||:||||||||
 496 LVNTSLGWPNGLALDLQEGKLYWGDAKTDKIEVINIDGTKRKTLLEDKLP 545

              .         .         .         .         .
 547 HIFGFTLLGDFIYWTDWQRRSIERVHKVKASRDVIIDQLPDLMGLKAVNV 596
     ||||||||||||||||||||||||||||||||||||||||||||||||||
 546 HIFGFTLLGDFIYWTDWQRRSIERVHKVKASRDVIIDQLPDLMGLKAVNV 595

              .         .         .         .         .
 597 AKVVGTNPCADRNGGCSHLCFFTPHATRCGCPIGLELLSDMKTCIVPEAF 646
     ||||||||||| ||||||||||||:||:|||||||||||||||||:||||
 596 AKVVGTNPCADGNGGCSHLCFFTPRATKCGCPIGLELLSDMKTCIIPEAF 645

              .         .         .         .         .
 647 LVFTSRAAIHRISLETNNNDVAIPLTGVKEASALDFDVSNNHIYWTDVSL 696
     |||||||.||||||||||||||||||||||||||||||||||||||||||
 646 LVFTSRATIHRISLETNNNDVAIPLTGVKEASALDFDVSNNHIYWTDVSL 695
```

FIG. 26B

Alignment of Human and Mouse Zmax1 (LRP5) Amino-Acid Sequences.

```
               .         .         .         .         .
 697 KTISRAFMNGSSVEHVVEFGLDYPEGMAVDWMGKNLYWADTGTNRIEVAR 746
     ||||||||||||||||:|||||||||||||||||||||||||||||||||
 696 KTISRAFMNGSSVEHVIEFGLDYPEGMAVDWMGKNLYWADTGTNRIEVAR 745
               .         .         .         .         .
 747 LDGQFRQVLVWRDLDNPRSLALDPTKGYIYWTEWGGKPRIVRAFMDGTNC 796
     ||||||||||||||||||||||||||||||||||||||||||||||||||
 746 LDGQFRQVLVWRDLDNPRSLALDPTKGYIYWTEWGGKPRIVRAFMDGTNC 795
               .         .         .         .         .
 797 MTLVDKVGRANDLTIDYADQRLYWTDLDTNMIESSNMLGQERVVIADDLP 846
     ||||||||||||||||||||||||||||||||||||||||||:|||||||
 796 MTLVDKVGRANDLTIDYADQRLYWTDLDTNMIESSNMLGQERMVIADDLP 845
               .         .         .         .         .
 847 HPFGLTQYSDYIYWTDWNLHSIERADKTSGRNRTLIQGHLDFVMDILVFH 896
     .|||||||||||||||||||||||||||||||||||||||||||||||||
 846 YPFGLTQYSDYIYWTDWNLHSIERADKTSGRNRTLIQGHLDFVMDILVFH 895
               .         .         .         .         .
 897 SSRQDGLNDCMHNNGQCGQLCLAIPGGHRCGCASHYTLDPSSRNCSPPTT 946
     ||||||||||:|.|||||||||||||||||||||||||||||||||||.|
 896 SSRQDGLNDCVHSNGQCGQLCLAIPGGHRCGCASHYTLDPSSRNCSPPST 945
               .         .         .         .         .
 947 FLLFSQKSAISRMIPDDQHSPDLILPLHGLRNVKAIDYDPLDKFIYWVDG 996
     ||||||| |||||||||| ||||:||||||||||||:|||||||||||||
 946 FLLFSQKFAISRMIPDDQLSPDLVLPLHGLRNVKAINYDPLDKFIYWVDG 995
               .         .         .         .         .
 997 RQNIKRAKDDGTQPFVLTSLSQGQNPDRQPHDLSIDIYSRTLFWTCEATN 1046
     |||||||||||||| :||| ||: .|||||||||||||||||||||||||
 996 RQNIKRAKDDGTQPSMLTSPSQSLSPDRQPHDLSIDIYSRTLFWTCEATN 1045
               .         .         .         .         .
1047 TINVHRLSGEAMGVVLRGDRDKPRAIVVNAERGYLYFTNMQDRAAKIERA 1096
     |||||||.|:||||||||||||||||.|||||||:|||||||:|||||||
1046 TINVHRLDGDAMGVVLRGDRDKPRAIAVNAERGYMYFTNMQDHAAKIERA 1095
               .         .         .         .         .
1097 ALDGTEREVLFTTGLIRPVALVVDNTLGKLFWVDADLKRIESCDLSGANR 1146
     .||||||||||||||||||||||||.||||||||||||||||||||||||
1096 SLDGTEREVLFTTGLIRPVALVVDNALGKLFWVDADLKRIESCDLSGANR 1145
               .         .         .         .         .
1147 LTLEDANIVQPLGLTILGKHLYWIDRQQQMIERVEKTTGDKRTRIQGRVA 1196
     |||||||||||:|||:||:|||||||||||||||||||||||||:||||.
1146 LTLEDANIVQPVGLTVLGRHLYWIDRQQQMIERVEKTTGDKRTRVQGRVT 1195
               .         .         .         .         .
1197 HLTGIHAVEEVSLEEFSAHPCARDNGGCSHICIAKGDGTPRCSCPVHLVL 1246
     ||||||||||||||||||||||||||||||||||||||||||||||||||
1196 HLTGIHAVEEVSLEEFSAHPCARDNGGCSHICIAKGDGTPRCSCPVHLVL 1245
               .         .         .         .         .
1247 LQNLLTCGEPPTCSPDQFACATGEIDCIPGAWRCDGFPECDDQSDEEGCP 1296
     ||||||||||||||||||||.|||||||||||||||||||.|||||||||
1246 LQNLLTCGEPPTCSPDQFACTTGEIDCIPGAWRCDGFPECADQSDEEGCP 1295
               .         .         .         .         .
1297 VCSAAQFPCARGQCVDLRLRCDGEADCQDRSDEADCDAICLPNQFRCASG 1346
     ||||.|||||||||||||||||||||||||||:|||:||||||||||.||
1296 VCSASQFPCARGQCVDLRLRCDGEADCQDRSDEANCDAVCLPNQFRCTSG 1345
               .         .         .         .         .
1347 QCVLIKQQCDSFPDCIDGSDELMCEITKPPSDDSPAHSSAIGPVIGIILS 1396
     ||||||||||||||| ||||||||||.|||||| ||||||||||||||||
1346 QCVLIKQQCDSFPDCADGSDELMCEINKPPSDDIPAHSSAIGPVIGIILS 1395
               .         .         .         .         .
1397 LFVMGGVYFVCQRVVCQRYAGANGPFPHEYVSGTPHVPLNFIAPGGSQHG 1446
     ||||||||||||||:||||.||.||||||||:|.||||||||||||||||
1396 LFVMGGVYFVCQRVMCQRYTGASGPFPHEYVGGAPHVPLNFIAPGGSQHG 1445
```

FIG. 26C

Alignment of Human and Mouse Zmax1 (LRP5) Amino-Acid Sequences.

```
              .         .         .         .         .
1447 PFTGIACGKSMMSSVSLMGGRGGVPLYDRNHVTGASSSSSSSTKATLYPP 1496
     ||.||:|:||:|||:||:||||:|||||||||||||||||||||||||||
1446 PFPGIPCSKSVMSSMSLVGGRGSVPLYDRNHVTGASSSSSSSTKATLYPP 1495

              .         .         .         .         .
1497 ILNPPPSPATDPSLYNMDMFYSSNIPATARPYRPYIIRGMAPPTTPCSTD 1546
     ||||||||||||||||:|:||||.|||||||||||:||||||||||||||
1496 ILNPPPSPATDPSLYNVDVFYSSGIPATARPYRPYVIRGMAPPTTPCSTD 1545

              .         .         .         .         .
1547 VCDSDYSASRWKASKYYLDLNSDSDPYPPPPTPHSQYLSAEDSCPPSPAT 1596
     ||||||| ||||.|||||||||||||||||||||||||||||||||||:|
1546 VCDSDYSISRWKSSKYYLDLNSDSDPYPPPPTPHSQYLSAEDSCPPSPGT 1595

              .
1597 ERSYFHLFPPPPSPCTDSS 1615
     |||| ||||||||||||||
1596 ERSYCHLFPPPPSPCTDSS 1614
```

FIG. 27A

Alignment of Human LRP5 and LRP6

Top = LRP5, Bottom = LRP6

Underlined = region marked for antibody production

Percent Similarity: 83.542 Percent Identity: 70.901

```
              .         .         .         .         .
   1 MEAAPPGPPWPLLLLLLLLLALCGCPAPAAASPLLLFANRRDVRLVDAGG 50
                :  :|  ||| |: ..   |.||||:|||||:|||||..
   1 ...........MGAVLRSLLA.CSFCVLLRAAPLLLYANRRDLRLVDATN 38

              .         .         .         .         .
  51 VKLESTIVVSGLEDAAAVDFQFSKGAVYWTDVSEEAIKQTYLNQTGAAVQ 100
     .| :.||||:|||||||||| ||.| :||.||||||||.| :|.|: .||
  39 GKENATIVVGGLEDAAAVDFVFSHGLIYWSDVSEEAIKRTEFNKTE.SVQ 87

              .         .         .         .         .
 101 NVVISGLVSPDGLACDWVGKKLYWTDSETNRIEVANLNGTSRKVLFWQDL 150
     |||:|||:|||||||||:|.||||||||||||||.||:|. |||||||:|
  88 NVVVSGLLSPDGLACDWLGEKLYWTDSETNRIEVSNLDGSLRKVLFWQEL 137

              .         .         .         .         .
 151 DQPRAIALDPAHGYMYWTDWGETPRIERAGMDGSTRKIIVDSDIYWPNGL 200
     ||||||||||. |:||||||||.|:|||||||||.| ||::|:|||||||
 138 DQPRAIALDPSSGFMYWTDWGEVPKIERAGMDGSSRFIIINSEIYWPNGL 187

              .         .         .         .         .
 201 TIDLEEQKLYWADAKLSFIHRANLDGSFRQKVVEGSLTHPFALTLSGDTL 250
     |:|.||||||||||||.|||:.||||. || ||.|||.||||||| :|.|
 188 TLDYEEQKLYWADAKLNFIHKSNLDGTNRQAVVKGSLPHPFALTLFEDIL 237

              .         .         .         .         .
 251 YWTDWQTRSIHACNKRTGGKRKEILSALYSPMDIQVLSQERQPFFHTRCE 300
     ||||| |:|| |||| ||:  :|| |.::|||||:.:||:|||   ..|:
 238 YWTDWSTHSILACNKYTGEGLREIHSDIFSPMDIHAFSQQRQPNATNPCG 287

              .         .         .         .         .
 301 EDNGGCSHLCLLSPSEPFYTCACPTGVQLQDNGRTCKAGAEEVLLLARRT 350
      ||||||||||:|| .||| |||||||.| :||:|||.||.|:|||||||
 288 IDNGGCSHLCLMSPVKPFYQCACPTGVKLLENGKTCKDGATELLLLARRT 337

              .         .         .         .         .
 351 DLRRISLDTPDFTDIVLQVDDIRHAIAIDYDPLEGYVYWTDDEVRAIRRA 400
     ||||||||||||||||||::||||||||||||:|||:||||||||||||.
 338 DLRRISLDTPDFTDIVLQLEDIRHAIAIDYDPVEGYIYWTDDEVRAIRRS 387

              .         .         .         .         .
 401 YLDGSGAQTLVNTEINDPDGIAVDWVARNLYWTDTGTDRIEVTRLNGTSR 450
     ::||||.| :|..:|..||||||||||||||||||||||||||||||| |
 388 FIDGSGSQFVVTAQIAHPDGIAVDWVARNLYWTDTGTDRIEVTRLNGTMR 437

              .         .         .         .         .
 451 KILVSEDLDEPRAIALHPVMGLMYWTDWGENPKIECANLDGQERRVLVNA 500
     |||:||||:|||||.|.|::|.|||||||| |||| |.||| :| ||||.
 438 KILISEDLEEPRAIVLDPMVGYMYWTDWGEIPKIERAALDGSDRVVLVNT 487

              .         .         .         .         .
 501 SLGWPNGLALDLQEGKLYWGDAKTDKIEVINVDGTKRRTLLEDKLPHIFG 550
     |||||||||||.:|||:||||||||||||:|.||| ||.|:|||:|||||
 488 SLGWPNGLALDYDEGKIYWGDAKTDKIEVMNTDGTGRRVLVEDKIPHIFG 537

              .         .         .         .         .
 551 FTLLGDFIYWTDWQRRSIERVHKVKASRDVIIDQLPDLMGLKAVNVAKVV 600
     ||||||::||||||||||||||| .|.|:||||||||||||||.|| :|:
 538 FTLLGDYVYWTDWQRRSIERVHKRSAEREVIIDQLPDLMGLKATNVHRVI 587

              .         .         .         .         .
 601 GTNPCADRNGGCSHLCFFTPHATRCGCPIGLELLSDMKTCIVPEAFLVFT 650
     |.||||: ||||||||:: |:: ||:||||:||:|||||||||||||:|.
 588 GSNPCAEENGGCSHLCLYRPQGLRCACPIGFELISDMKTCIVPEAFLLFS 637
```

FIG. 27B

Alignment of Human LRP5 and LRP6

```
              .         .         .         .         .
 651 SRAAIHRISLETNNNDVAIPLTGVKEASALDFDVSNNHIYWTDVSLKTIS 700
     .||.|:|||||||||:||||||||||||||||||.:|:|||||:||||||
 638 RRADIRRISLETNNNNVAIPLTGVKEASALDFDVTDNRIYWTDISLKTIS 687

              .         .         .         .         .
 701 RAFMNGSSVEHVVEFGLDYPEGMAVDWMGKNLYWADTGTNRIEVARLDGQ 750
     |||||||.:||||||||||||||||||:||||||||||||||||.:||||
 688 RAFMNGSALEHVVEFGLDYPEGMAVDWLGKNLYWADTGTNRIEVSKLDGQ 737

              .         .         .         .         .
 751 FRQVLVWRDLDNPRSLALDPTKGYIYWTEWGGKPRIVRAFMDGTNCMTLV 800
      ||||||:|||.||.|||||..|::|||||||||:| || |||.:  |||
 738 HRQVLVWKDLDSPRALALDPAEGFMYWTEWGGKPKIDRAAMDGSERTTLV 787

              .         .         .         .         .
 801 DKVGRANDLTIDYADQRLYWTDLDTNMIESSNMLGQERVVIADDLPHPFG 850
     ..|||||:||||||..||||||||||:|||||||| :| |||||||||||
 788 PNVGRANGLTIDYAKRRLYWTDLDTNLIESSNMLGLNREVIADDLPHPFG 837

              .         .         .         .         .
 851 LTQYSDYIYWTDWNLHSIERADKTSGRNRTLIQGHLDFVMDILVFHSSRQ 900
     |||| ||||||||. :|||||:||||.|||:||||||:||||||||||||
 838 LTQYQDYIYWTDWSRRSIERANKTSGQNRTIIQGHLDYVMDILVFHSSRQ 887

              .         .         .         .         .
 901 DGLNDCMHNNGQCGQLCLAIP.GGHRCGCASHYTLDPSSRNCSPPTTFLL 949
     .|:|:|  .||:|::||||:| ||  |||:.||.|::..|.||:||||||
 888 SGWNECASSNGHCSHLCLAVPVGGFVCGCPAHYSLNADNRTCSAPTTFLL 937

              .         .         .         .         .
 950 FSQKSAISRMIPDDQHSPDLILPLHGLRNVKAIDYDPLDKFIYWVDGRQN 999
     |||||||.||: |:|:|||:|||:|:||||:||||||||| :||:|:|||
 938 FSQKSAINRMVIDEQQSPDIILPIHSLRNVRAIDYDPLDKQLYWIDSRQN 987

              .         .         .         .         .
1000 .IKRAKDDGTQPF.VLTSLSQGQNPDRQPHDLSIDIYSRTLFWTCEATNT 1047
      |::|.:||.|.| |:.|  .:|| : ||.||||||||| ::|||||||.
 988 MIRKAQEDGSQGFTVVVSSVPSQNLEIQPYDLSIDIYSRYIYWTCEATNV 1037

              .         .         .         .         .
1048 INVHRLSGEAMGVVLRGDRDKPRAIVVNAERGYLYFTNMQDRAAKIERAA 1097
     ||| ||.| .:||||:|:.|:|||||||:|:||:||||:|:|.:||||||
1038 INVTRLDGRSVGVVLKGEQDRPRAIVVNPEKGYMYFTNLQERSPKIERAA 1087

              .         .         .         .         .
1098 LDGTEREVLFTTGLIRPVALVVDNTLGKLFWVDADLKRIESCDLSGANRL 1147
     |||||||||| .|| :|:||.:|. ||||||.|.||:||||:|||||||:
1088 LDGTEREVLFFSGLSKPIALALDSRLGKLFWADSDLRRIESSDLSGANRI 1137

              .         .         .         .         .
1148 TLEDANIVQPLGLTILGKHLYWIDRQQQMIERVEKTTGDKRTRIQGRVAH 1197
     .|||.||:||:|||:::. |||||:||||||:::.|. : ||::|:|:|:
1138 VLEDSNILQPVGLTVFENWLYWIDKQQQMIEKIDMTGREGRTKVQARIAQ 1187

              .         .         .         .         .
1198 LTGIHAVEEVSLEEFSAHPCARDNGGCSHICIAKGDGTPRCSCPVHLVLL 1247
     |.:||||.|:.|:|:..||||.|||||||||:.|||||.|||||:|||||
1188 LSDIHAVKELNLQEYRQHPCAQDNGGCSHICLVKGDGTTRCSCPMHLVLL 1237

              .         .         .         .         .
1248 QNLLTCGEPPTCSPDQFACATGEIDCIPGAWRCDGFPECDDQSDEEGCPV 1297
     |: |.|||||||||:||.| ||||||||.|||||||.||:|:||| .|||
1238 QDELSCGEPPTCSPQQFTCFTGEIDCIPVAWRCDGFTECEDHSDELNCPV 1287

              .         .         .         .         .
1298 CSAAQFPCARGQCVDLRLRCDGEADCQDRSDEADCDAICLPNQFRCASGQ 1347
     ||..||.||.|||:|  |||:|:|:|||:||| :|:.:|| :|||||.||
1288 CSESQFQCASGQCIDGALRCNGDANCQDKSDEKNCEVLCLIDQFRCANGQ 1337

              .         .         .         .         .
1348 CVLIKQQCDSFPDCIDGSDELMCEITKPPSDDSPAHSSAIGPVIGIILSL 1397
     |:  ...||  .|| | |||| |  |..|   .|. ...:|.|||:|:.:
1338 CIGKHKKCDHNVDCSDKSDELDCYPTEEP...APQATNTVGSVIGVIVTI 1384
```

FIG. 27C

Alignment of Human LRP5 and LRP6

```
              .         .         .         .         .
1398 FVMGGVYFVCQRVVCQRYAGANGPFPHEYVS.GTPHVPLNFIAPGGSQHG 1446
     || |.|||:|||::|.|  |..:.:.::||  |.: |||.:::..:|  |
1385 FVSGTVYFICQRMLCPRMKGDGETMTNDYVVHGPASVPLGYVPHPSSLSG 1434

              .         .         .         .         .
1447 PFTGIACGKSMMSSVSLMGGRGGVPLYDRNHVTGASSSSSSSTKATLYPP 1496
     .:.|:. ||||:||:|:|||.:|.| |||.||||||||||||||:|.:|:
1435 SLPGMSRGKSMISSLSIMGGSSGPP.YDRAHVTGASSSSSSSTKGTYFPA 1483

              .         .         .         .         .
1497 ILNPPPSPATDPSLYNMDMFYSSNIPATAR..PYRPYIIRGMAPPTTPCS 1544
     ||||||||||:.| |.|:: |||| |.| |  .|||| .| :||||||||
1484 ILNPPPSPATERSHYTMEFGYSSNSPSTHRSYSYRPYSYRHFAPPTTPCS 1533

              .         .         .         .         .
1545 TDVCDSDYSASRWKAS....:KYYLDLNSDSDPYPPPPTPHSQYLSAE.. 1587
     ||||||||.:||:..|      |  ||| ||:| ||||||:|||||||
1534 TDVCDSDYAPSRRMTSVATAKGYTSDLNYDSEPVPPPPTPRSQYLSAEEN 1583

              .         .         .
1588 .DSCPPSPATERSY.FHLFPPPPSPCTDSS 1615
      :|||||| |||||  ||:|||||||||||
1584 YESCPPSPYTERSYSHHLYPPPPSPCTDSS 1613
```

Rodent 4-point bending device to measure effect of mechanical load on tibia

(MP Akhter & DM Cullen, Creighton University)

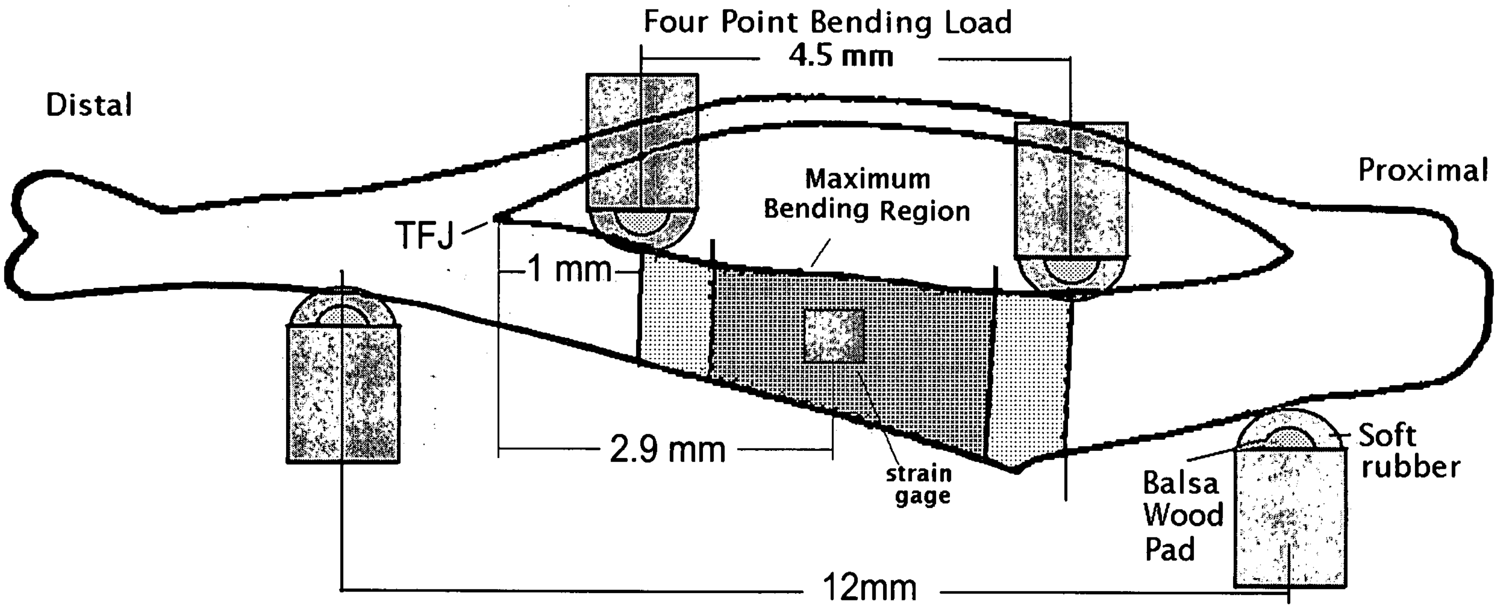


FIG. 28

Enhanced bone formation in HBM1 transgenic mice: *Response to mechanical loading*

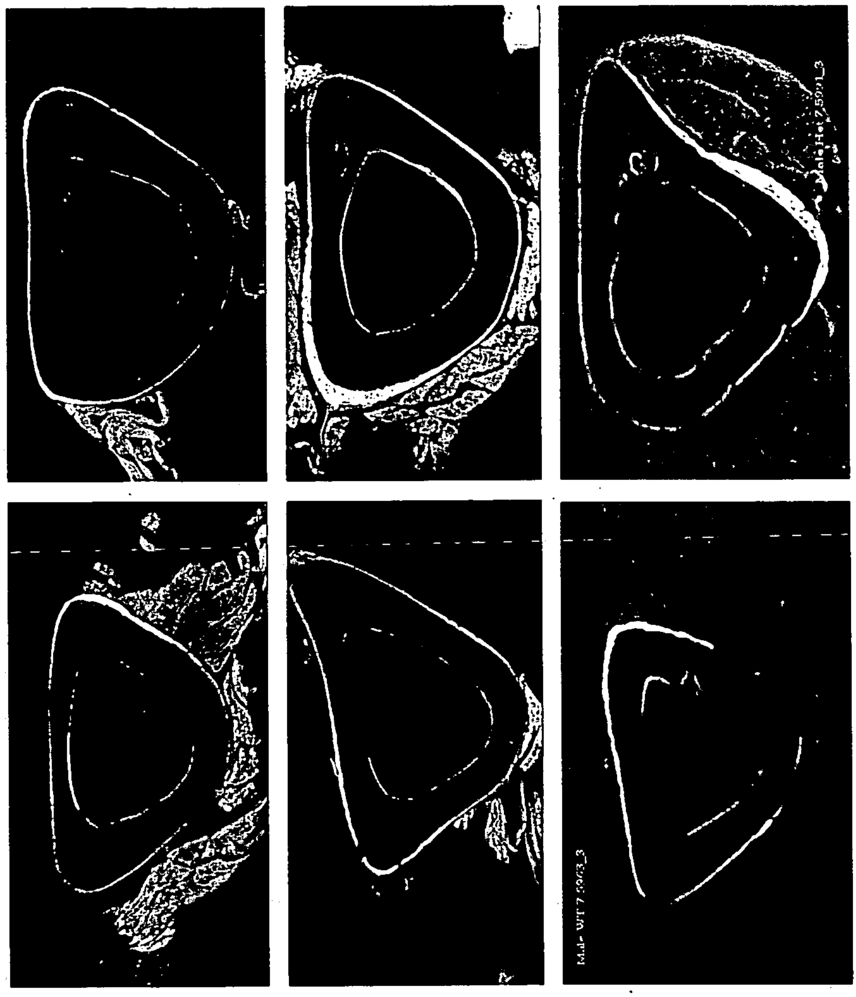


FIG. 29